Comprehensive Manuals in Pediatrics

Series Editors

Michael Katz

E. Richard Stiehm

Pediatric Infectious Diseases
for the Practitioner

Melvin I. Marks, M.D.

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To those who *care* for children

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Series Foreword

Comprehensive Manuals in Pediatrics are designed to broaden the practitioner's clinical scope by providing a wide range of diagnostic and management skills ordinarily considered to be the exclusive domain of the specialists. Although the series as a whole constitutes a comprehensive text in pediatrics, each volume stands on its own as a self-contained reference for the busy practitioner.

In order to maintain a uniform style and coverage of each subject, each manual is usually written by no more than one or two authors. Each author is an acknowledged expert in his or her field and provides a comprehensive, up-to-date account of the topic under discussion. Practically oriented, each volume offers concise guidelines and courses of treatment.

Michael Katz
E. Richard Stiehm

Preface

The preface—my opportunity to rationalize this labor, titillate the reader, philosophize or otherwise self-indulge. I'll take full advantage.

Why write a book? After fifteen years' experience as an infectious disease consultant, teacher and researcher, I feel it is time to speak out! I have spent the majority of my waking hours thinking, reading and writing about childrens' infectious disease problems, have amassed a veritable Fort Knox of publications on the subject and have been reasonably outspoken. Yet the field continues to progress with reckless speed and the gaps between our knowledge and effective communication of new information remain wide. I am eager to accept more responsibility for teaching yet my audience has been limited. This, added to my frustration with multi-authored texts, prompted me to write this book.

Who is the book intended for? This book is intended for and dedicated to those who will take the time to read it - my comrades in arms! Facetious as it may seem, readers are not as frequent as purchasers and purchasers not as frequent as health care providers. I hope the contents will appeal to students, primary care clinicians and their assistants, and trainees and practitioners in infectious diseases and clinical microbiology. They see a patient, have the courage to make a diagnosis, to change it if appropriate events arise, to withhold antibiotics, to admit their lack of knowledge, to seek help in these pages and from their colleagues, and to dedicate themselves to continue to learn from their patients and each other.

What is the book about? This book concerns common pediatric infectious disease problems. The system approach is used (e.g., respiratory, gastrointestinal, skin infections) and is considered in terms of viral, bacterial, and fungal causes of illness. Mycoplasma, protozoa, chlamydia, parasites and rickettsia are also included where appropriate, as are noninfectious causes. I give special consideration to immunizations, antimicrobial therapy and to particular groups, such as newborns. I refer to problems that I have seen repeatedly for purposes of teaching and illustration. Let's face it, many of the common infectious diseases of children are self-limiting and benign and can be diagnosed and handled in several fashions, often of equal validity. The most important lessons for the doctor are often provided by the most difficult and unusual cases. Thus I am not taking an ivory tower view of infectious diseases, but rather trying to use the type of case a consultant like myself might see to illustrate principles of diagnosis and management applicable to common problems in practice.

How will this book achieve the goals of teaching students and helping practitioners? I often judge a book by consulting it several times in reference to specific problems about my patients or questions raised by students. After several attempts to consult the index to guide me to the information I am seeking, I can usually begin to evaluate the practical usefulness of the text. Drawing upon that experience, I hope the index of this book proves to be replete with useful citations so that readers may easily be guided to informative, well organized content. Emphasis on clinical presentation, and liberal use of tables for listing causes, differential diagnoses, diagnostic aids and therapies should be especially helpful. Recent references are offered throughout the text for those interested in additional reading and to support more contentious statements.

Finally, no preface would be complete without a philosophical note. When I began to write this book, I felt like an explorer embarking on a new journey. It was with a mixture of excitement and apprehension that I set sail, hoping to effectively bridge the gap between the microbiological sciences and clinical infectious diseases. I hope this has been a successful journey.

Melvin I. Marks

Acknowledgement

Writing a single-authored textbook is like having a child. This one was inspired by my teachers and role models, Henry Kempe, Keith Drummond, Mary Ellen Avery and Theodore Eickhoff. The opportunity was provided by Michael Katz, E. Richard Stiehm and Springer-Verlag. The long arduous gestation required much love and understanding from my wife Susan, and my children, Suzanne, Jennifer and Daniel. Birth was facilitated by expert care from Joyce Bagan, Rose Stursa and Harris Stutman. Finally, I acknowledge the readers who will share the reward, but also the responsibility for this book's future growth and development.

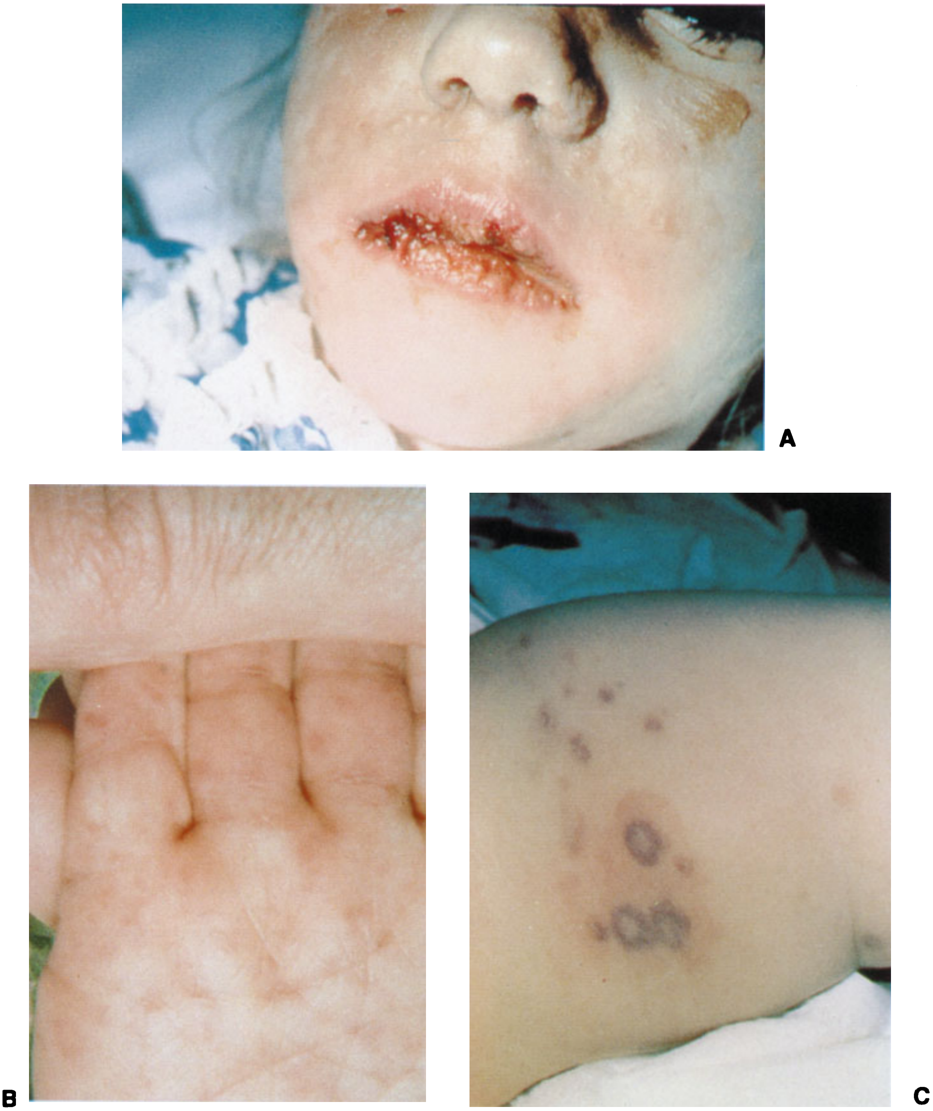


Figure 2-4. Three manifestations of antibiotic-associated erythema multiforme. **A**: Mucosal ulceration. **B**: Palmar rash. **C**: Hemorrhagic target lesions (see p. 44).

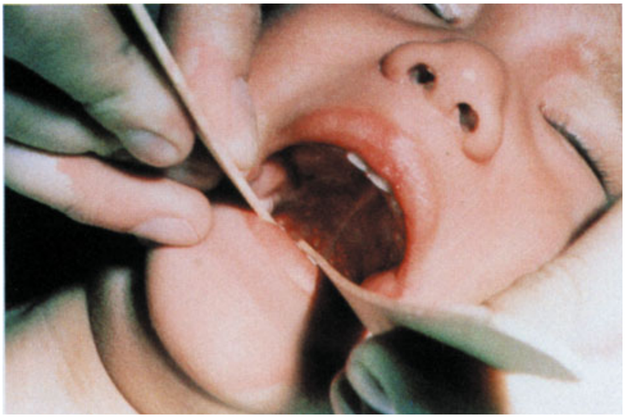


Figure 4-1. Herpangina lesions (white papules on a red base) on posterior palate (see p. 223).

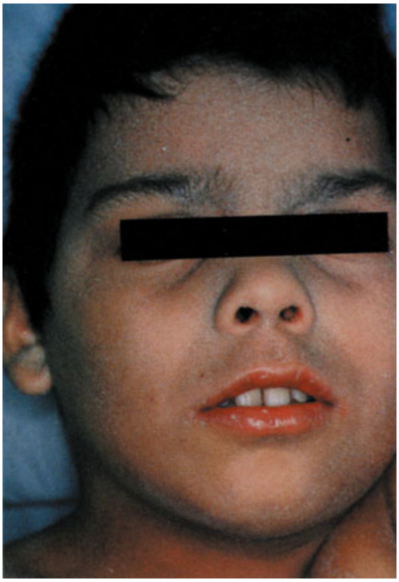


Figure 6-3. Scleral and cutaneous jaundice in patient with acute hepatitis (see p. 437).

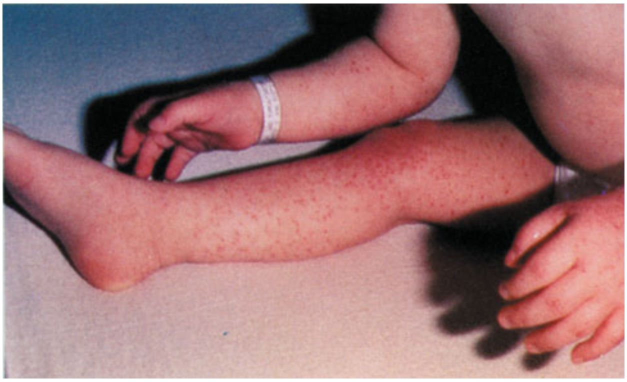
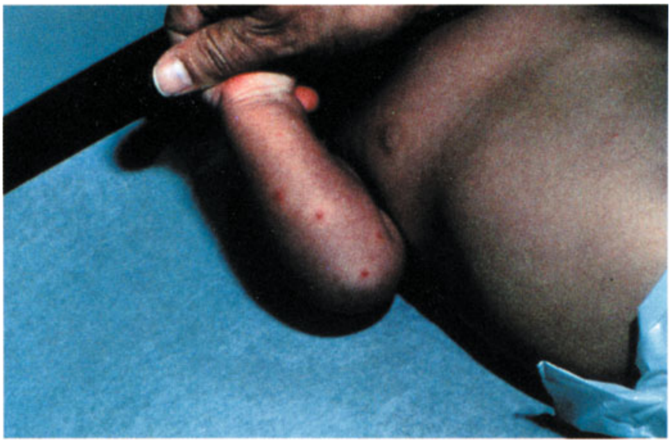
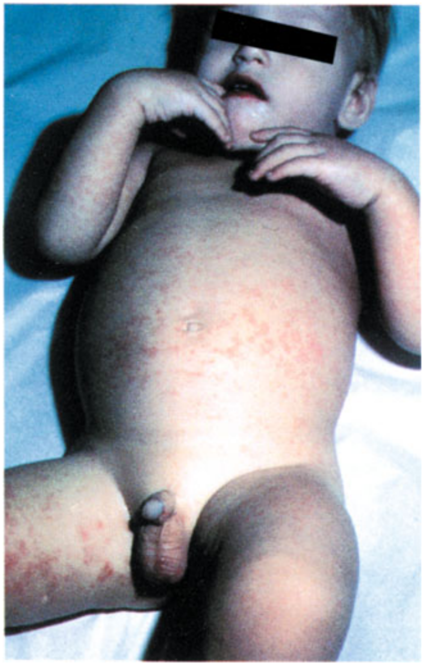


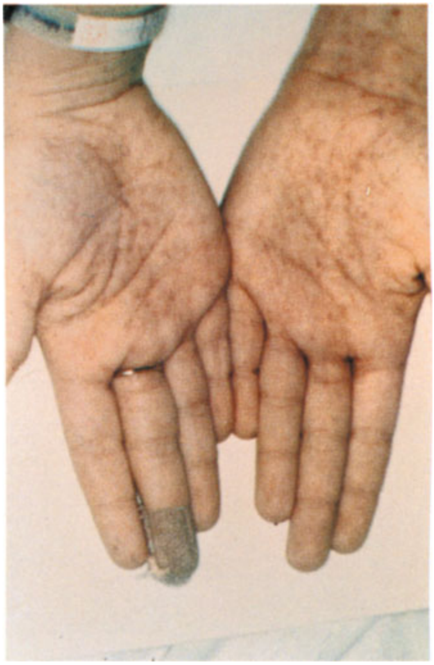
Figure 6-4. Papular acrodermatitits of Gianotti disease (see p. 437).



7-1a



7-1b



7-5

Figure 7-1. Cutaneous manifestations of ECHO virus 11 infection in two infants. (Courtesy of Dr. B. Brann.) (See p. 478).

Figure 7-5. Atypical measles rash on palms (see p. 485).

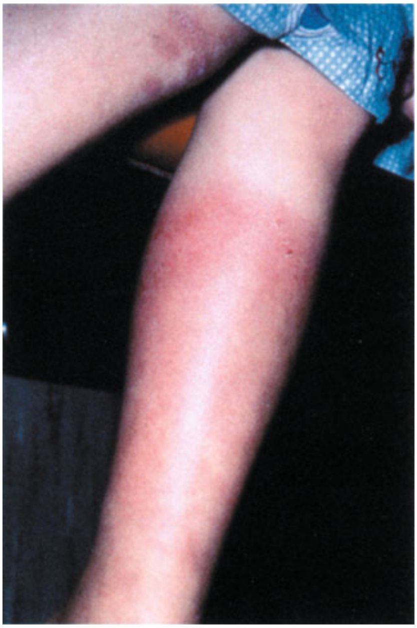


Figure 7-15. Streptococcal cellulitis (see p. 513).

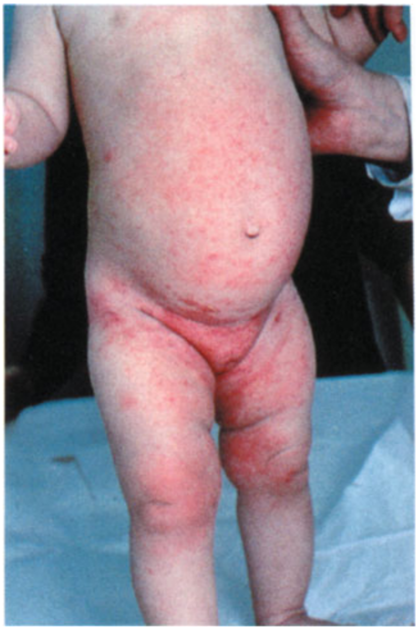


Figure 7-22. Dermatitis due to *Epidermphyton floccosum*. (Courtesy of Dr. B. Brann.) (See p. 537).

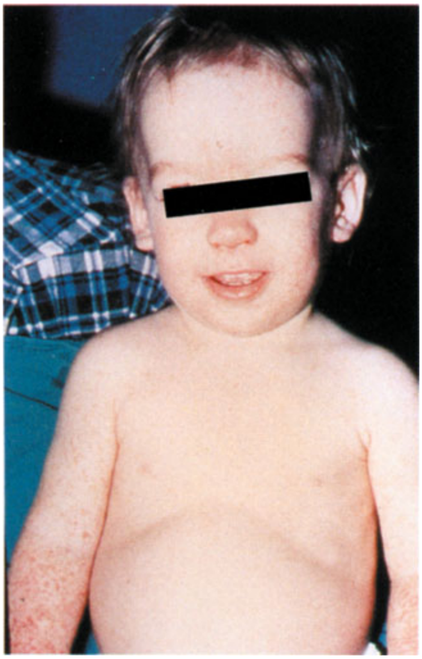


Figure 12-3. Skin eruption after the administration of ampicillin in a patient with infectious mononucleosis (see p. 737).

1

Pediatric Immunizations

General (Table 1-1)

The following comments are intended as guidelines and attempt to summarize the current scientific evidence. It is almost impossible to formulate a set of recommendations for immunization that will be universally useful, as many of the situations encountered in immunization procedures cannot be predicted accurately. Geographic areas or populations of high endemicity, as well as epidemic situations, may require different immunization practices.

International Travel[112]

A complete list of countries with their specific immunization requirements is contained in the U.S. Dept. HEW Publication No. (CDC) 79-8280 available from the U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Atlanta, GA 30333. Because of their side effects, typhoid, plague, and cholera vaccines are best given at least 4 weeks apart.

Pregnancy[100]

Polio and yellow fever immunizations are indicated for travel or residence in endemic areas or during epidemics. Mumps, rubella, and measles vaccines are contraindicated in pregnancy. Vaccines used during pregnancy should be free of impurities such as blood group antigens that may induce autoimmune hemolysis in the newborn.[21] Killed virus and bacterial vaccines (e.g., rabies, Salk polio, typhoid), bacterial products (e.g., tetanus toxoid), and immune globulin present no special problems during pregnancy.

Hypersensitivity[28]

History of egg (or other vaccine component) allergy contraindicates immunization with typhus, Rocky Mountain spotted fever, rabies (DEV), and yellow fever vaccine; influenza vaccine is much purer and is probably safe in persons able to eat eggs without adverse reactions; an immediate hypersensitivity scratch test, utilizing the vaccine as antigen, may also be used. Hypersensitivity reactions are extremely rare in egg-allergic patients receiving measles (see Measles), and mumps vaccines.

Malignancies/Immunosuppression

In general, live vaccines should be avoided in immunosuppressed patients and in those with malignancies. Antibody responses to diphtheria, tetanus, pertussis (DTP) and inactivated polio virus are lower than those of normal children but still protective.[162]

Seizures

Approximately 50% of children develop fever within 48 h of DTP immunization and 1/1750 have a seizure.[42] Brief self-limited seizures or hypotonic/hyporesponsive episodes with no sequelae were noted in 18 of 15,752 infant vaccinees.[42] A survey of neurologic reactions in 516,276 children immunized from 1959 to 1965 in Sweden[155] revealed an incidence of approximately 1/3600. Neurologic complications within the first 24 h after immunization and in patients with intercurrent infection are common,[135] but reported rates of pertussis vaccine complications are extremely variable.[94] Seizures were also studied after all immunizations in the offspring of approximately 54,000 pregnant women enrolled in the United States National Institute of Neurological and Communicative Disorders and Strokes Collaborative Perinatal Project.[74] Approximately 2766 children had seizures within the first 7 years of life; 39 of these (1.4%) occurred within 2 weeks of immunization. In all but one case these seizures were associated with high fever, lasted less than 30 min, and had a benign outcome. In one-half of the cases there was a personal or family history of febrile convulsions. Only one child had a significant long-term deficit, consisting of a speech disorder. Thus, the majority of seizures associated with immunization are benign and rare.

The risks of encephalopathy after pertussis infection, and of neurologic injury due to natural infection with tetanus, diphtheria, mumps, measles, and polio are much greater than after immunization. Nevertheless, some precautions are indicated when administering these vaccines. These should include avoiding immunizations with DTP for at least 6 months after resolution of acute neurologic injury from whatever cause. In most cases, however, the decision should be individualized, weighing the risks of exposure to natural infection versus the known risks of immunization.

TABLE 1-1. Immunizing Schedule

Age	*Product*
2 months	DTP[a] TOPV[b]
4 months	DTP-TOPV
6 months	DTP
13–15 months	Tuberculin test, measles[c]
1–12 years	Rubella[d] Mumps[d]
18 months	DTP-TOPV
4–6 years	DTP-TOPV
14–16 years	Td[e]

[a] Diphtheria, tetanus, pertussis.
[b] Trivalent oral polio vaccine; 6-month booster is recommended only in areas endemic for poliomyelitis.
[c] Measles vaccine should not generally be given to children under 1 year of age. Tuberculin screening of well children may be done at the same time as measles, rubella, or mumps vaccination,[118] and may be repeated annually depending on the risk of exposure of the child and on the prevalence of tuberculosis in the population.
[d] May be given at 13–15 months as measles-rubella, mumps-rubella, or measles-mumps-rubella.
[e] Combined tetanus and diphtheria toxoids (adult type) for those over 6 years of age.

In many circumstances, the risk of vaccine-associated seizures can be minimized by reducing the expected febrile response through use of antipyretics. In others, the risk of seizures associated with vaccine still justifies their use, considering the high risk of acquisition of natural disease.

Conventional Vaccines

B.C.G.

B.C.G. (Bacille-Calmette-Guerin vaccine) is a live mycobacterial vaccine partially effective in reducing the frequency, morbidity, and mortality associated with tuberculosis.[41] It is particularly effective in "high-risk" areas in which new cases of tuberculosis are frequently seen and when other general measures to prevent tuberculosis have not been effective. Certain large city ghetto areas in North America, as well as Indian and Eskimo populations, may well fit these criteria. B.C.G. has also been used in newborns, in those with recurrent or prolonged exposure to tuberculosis, and in populations where the frequency of skin test conversion exceeds 1% annually.[29]

If the vaccine is used, it should be quality-controlled and followed by quantitative tuberculin skin testing (Mantoux) performed 2 months after immunization to ascertain the degree of skin test reactivity. If the skin reaction is negative, repeated vaccination is recommended. Any significant increase in this skin test reaction with an equivalent amount of tuberculin upon further testing can be used to guide the physician to cases of recent conversion due to active tuberculosis and/or atypical mycobacterial disease. Local lymphadenopathy is seen in about 2% of patients immunized with B.C.G.[38] Other rare complications include osteomyelitis,[20] lupoid reactions, anaphylaxis,[69] and disseminated B.C.G. infection, sometimes fatal.[103]

Diphtheria, Tetanus, Pertussis (DTP)[116] (see also Tetanus)

This product contains alum-precipitated diphtheria and tetanus toxoids and killed pertussis bacteria. The advantages of this preparation over fluid or single antigens are: (1) greater antigenic stimulation with a more satisfactory pertussis response in the early months of infancy, and (2) decreased incidence of systemic reactions. Disadvantages include local reactions and a slightly increased interval between vaccination and antibody response. Preparations are administered deep subcutaneously in the anterior side of the thigh or at the insertion of the deltoid. Only fluid toxoid should be given intradermally.

On completion of the recommended three basic immunizations, approximately 90% of infants will have relative immunity to pertussis, while protection against diphtheria and tetanus will approach 99%.[18] If a dose is missed because of illness, etc., the second or third dose may be given later without restarting immunization.[131] After two diphtheria immunizations and a booster 1 year later, 88% still have protective antibody at 13–14 years of age.[148] Primary immunization of preterm infants can begin at 2 months of age.[16] Antitoxin concentrations are not reduced in malnourished children.[62]

Pertussis vaccine is generally effective but has side effects.[115] Local pain, swelling, fever, and erythema occur in approximately one-half of DTP recipients. Prior administration of acetaminophen may decrease fever after the primary dose.[123] Paroxysmal supraventricular tachycardia may be precipitated by DTP[128] (see also Seizures above).

DTP vaccine efficacy varies from 63 to 77%. Some vaccinees may be asymptomatically colonized with Bordetella but the risk of spread from these subjects is unknown.[23] In general, DTP reduces the severity and duration of illness, and decreases communicability in vaccinees.[65]

When the rates of pertussis are low, a recent history of convulsions in the patient should preclude pertussis vaccination. Otherwise, evidence is lacking to support exact guidelines for pertussis vaccination in children with active cerebral damage. In such infants I recommend that immunization procedures be delayed until 6 months after active cerebral irritation (convulsions, meningitis, etc.) has subsided. The current estimate of risk of brain damage after pertussis vaccine is 1/310,000 injections.[50] If a convulsion, severe febrile reaction, or thrombocytopenia occurs after immunization, no further pertussis vaccine should be given. Immunization should be continued with DT (adjuvant added) in reduced dosage. If the indication for pertussis immunization is strong (even in patients over 6 years of age), use DTP adsorbed or pertussis vaccine adsorbed in reduced dosage.

DT-Adult (see also Tetanus)

This is a combination specifically altered to contain about 1/10 the amount of diphtheria toxoid in DTP in order to reduce undesirable reactions. This type of preparation should be the only one used after the age of 6 years. The recommended interval between boosters is 10 years and includes administration into adulthood.[106] Local reactions (erythema, induration around the inoculation) are encountered in approximately 10% of older children and adults receiving primary doses.[124]

Hepatitis (Table 1-2)

Hepatitis A is an infection caused by a small 27-nm virus not yet fully characterized. Although morbidity is age-related and mortality quite low (< 1%), there is considerable discomfort and inconvenience associated with the illness in school-age children in particular. The incubation period is 15–45 days, with an average of about 1 month. Virus is excreted in the stool during late incubation and the early prodromal phase of illness. The period of maximal infectivity occurs during the 2-week period before the onset of jaundice; there is a short period of viremia. Immune serum globulin from normal adult human donors is recommended to prevent hepatitis A whenever exposure suggests the likelihood of infection. The efficacy of this product is greatest within the first 1–2 weeks after exposure. In such cases, illness is prevented by passive immunization in 80–90% of those exposed. Because immunization may not prevent inapparent infection, longlasting natural immunity may result,[75] but excretion of virus in the stool may also occur. The recommended dosage for postexposure prophylaxis is 0.02 ml/kg and is recommended for household contacts who have not already had hepatitis A, those exposed to the same common source previously shown to contain hepatitis A (i.e., food, water, or other vehicle), and in infants attending day-care centers, their families, and their caretakers. Older children in school, institutional contacts, and hospital contacts, as well as supervisory personnel, should receive this material only when a demonstrated outbreak has occurred. It is not recommended for use in those individuals casually exposed to

TABLE 1–2. Passive Immunization (Antibody Prophylaxis and/or Therapy)

Disease	*Product*	*Prophylactic use*	*Therapeutic use*	*Dosage and Route*	*Indications*	*Hazards*
Agammaglobulinemia	Human γ-globulin (ISG) (165 mg/ml)	X	X	300–400 mg/kg IV every 3–4 weeks. Larger doses may be used IV.	Recurrent bacterial infections	Allergic reactions with repeated use
Botulism	Horse serum trivalent (ABE)		X	5–10,000 units, IV	Suspected or proven botulism	HSA, SS
Diphtheria	Horse serum		X	40–100,000 units IV	Suspected diagnosis	HSA, SS
Hepatitis A	ISG	X		0.02 ml/kg (maximum 5 ml) for postexposure prophylaxis and 0.05 ml/kg for preexposure. Repeat 2 ml dose q 3 months or 5 ml dose q 5 months IM or IV.	Exposure to hepatitis A. See text	
Hepatitis B	Hepatitis B immune globulin (HBIG)—human	X		0.06 ml/kg (maximum 5 ml), repeated in 1 month IM	See text	Allergic reactions (increased risk in patients with IgA deficiency). Local pain

Measles (rubeola)	ISG	X			0.2 ml/kg IM or IV	Exposure to measles
Mumps	Mumps immune γ-globulin (human)	X(?)			3–5 ml	Susceptible adults—efficacy doubtful[26]
Pertussis	Pertussis immune γ-globulin (human)	X(?)		X(?)	T:2.5 ml IM on alternate days for 3 doses	No prophylactic effect in children < 5 years.[121] No therapeutic effect in paroxysmal stage[7]
Rabies	Human rabies immune globulin (RIG)[70,142]	X			20 units/kg to maximum of 3000 units IM. (infiltrate wound with ¼ to ½ dose)	See text
Tetanus	Human tetanus γ-globulin[111]	X	X		P:4 units/kg to maximum of 250 (500 units adult) T:130 units/kg to 5000 units IM (infiltrate wound with ¼ to ½ dose)	Suspected diagnosis. Nonimmunized patient with wound

(*Continued*)

TABLE 1-2. Continued

Disease	*Product*	*Prophylactic use*	*Therapeutic use*	*Dosage and Route*	*Indications*	*Hazards*
Varicella (Chickenpox)	Convalescent plasma from pts. with recent herpes zoster.	X	X	10 ml/kg IV	VZIG prevents or modifies varicella in immunocompromised patients.[174] Prematures may need smaller doses (e.g., 1.25 ml).	
	*ZIG	X		5 ml IM		
	**VZIG	X		Patients ≤ 10 kg—125 units (2.5 ml) Patients 11–20 kg—250 units (5 ml) Patients 21–30 kg—375 units (7.5 ml) Patients 31–40 kg—500 units (10 ml) Patients ≥ 41 kg—625 units (12.5 ml)		

Abbreviations used: HSA, Horse serum anaphylaxis; IM, Intramuscular; IV, Intravenous; P, Prophylactic; SS, Serum sickness; T, Therapeutic; **VZIG, Varicella-zoster immune globulin; *ZIG, Zoster immune globulin.

sporadic cases. Preexposure prophylaxis is recommended for individuals exposed to nonhuman primates, and for those travelling to areas of the world in which the risk of exposure to infected persons is extremely high, despite conventional hygienic and isolation measures. For these purposes 0.05 ml/kg, to be repeated every 4 months, is recommended.

Hepatitis B is caused by a 42-nm virus and some of the manifestations of disease are due to antigen-antibody complexes. The morbidity of this condition is higher than for hepatitis A, and this risk increases with age. The incubation period ranges from 60 to 180 days. The parenteral route is the most common one for transmission of illness, but percutaneous and mucosal introduction of serum or other infected body fluids may also occur; infections after sexual contact and via vectors or inanimate environmental surfaces have also been recorded.

Hepatitis B immune globulin, in a dosage of 0.06 ml/kg—maximum 5 ml (2 doses, 1 month apart), should be considered for use in those exposed to patients with acute hepatitis B or to patients who are chronic carriers.[136] The transmission may be percutaneous, oral, mucosal, sexual, or neonatal. A regimen of 2 ml every 6 weeks for the first 6 months of life has been recommended for newborns[82]; however, a three-dose course combined with vaccination is preferred (see Chapter 3). Although the presence of *e* antigen in the serum appears to correlate with infectivity in patients with chronic disease or carriage, it is also recommended that hepatitis B immune globulin be administered to newborns exposed to carriers with antibody to *e* antigen and to those who lack DNA polymerase activity. Repeated administration of hepatitis B immune globulin at monthly intervals should also be considered for use in hemodialysis units and in certain populations (i.e., institutions for the mentally retarded) where demonstrated transmission of hepatitis B has occurred. Again, active vaccination is preferred. It is probable that the administration of hepatitis B immune globulin prolongs the incubation period in some cases. The addition of hepatitis B immune globulin to Factor IX complex concentrate may reduce the infectivity of that product.[158]

There are no major toxic effects of hepatitis B immune globulin apart from discomfort at the site of the intramuscular injection and rare hypersensitivity reactions. The globulin should not be injected intravenously because of the possibility of severe hypersensitivity reactions. Persons with isolated immunoglobulin A deficiency are more prone to develop antibodies to immunoglobulin A and may be at higher risk for hypersensitivity reactions. The induction of immune complexes is a potential concern, but reactions have not been observed. The efficacy of hepatitis B immune globulin varies from 40 to 70%. Its use, therefore, should not detract from the practice of careful hygienic and isolation procedures for the prevention of spread of this disease.

Hepatitis B vaccine is composed of formalin-inactivated HBsAg particles from the plasma of carriers. It has been found safe and effective in homosexuals[157] and immunogenic in hemodialysis patients[156] and in newborns.[10] Moreover, when three doses were given to infants at 1-month intervals, there were no ill effects, immunogenicity was not reduced by preexisting maternal antibody, and the incidence of HBŝAg carriage was markedly reduced in susceptible children.[105] In subjects over 1 year of age, the second and third doses of vaccine are given 1 and 6 months after the first dose. Each dose is 2 ml (40 μg) for adults, and 0.5 ml for children under 10 years of age.[31] The vaccine is indicated for high-risk populations including male homosexuals, selected health and laboratory personnel, infants of HBŝAg-positive mothers, renal dialysis patients, institutionalized patients and their attending staff, patients requiring repeated blood transfusions, household contacts of HBŝAg-positive subjects, and children in areas of high hepatitis B virus endemicity.[2] Other candidates may include users of illicit injectable drugs, sexual and household contacts of acute hepatitis B cases, and subjects accidentally receiving needlesticks from HBŝAg-positive patients.[31] Healthy subjects in these groups (except newborns) should be screened for immunity (the presence of anti-HBŝ and/or anti-HBĉ) before vaccination.[134] In a recent survey, 6.3% of hospital workers had anti-HBŝ alone, while 3.6% had only anti-HBĉ.[64] Immunization of HB_sAg-positive infants with hepatitis B vaccine is safe but inefficient.[11]

Reactions to hepatitis B vaccine have been mild: sore arm (15%), fever (3%), headache (3%), fatigue (2%), nausea (2%), malaise (1%), myalgia (1%), arthralgia (0.5%), and nodules after subcutaneous injection, and there has been no unexpected incidence of acquired immunodeficiency syndrome (AIDS).[36] Although polyneuropathy has been described in a vaccine recipient, it is unclear whether hepatitis B vaccine was causative.[138]

Non-A, non-B (NANB) hepatitis[140] either may follow blood transfusion (approximately 90% of posttransfusion cases) or occur sporadically (25–50% of cases in U.S.). The diagnosis is made by exclusion of type A and type B hepatitis as well as hepatitis due to Ebstein-Barr virus, cytomegalovirus, toxoplasmosis and other toxic, metabolic, and infectious causes. Elevation of alanine aminotransferase (ALT) in the blood is consistent with the diagnosis and its absence usually argues against it. There is no vaccine currently available to prevent this type of hepatitis nor is the role of immune globulin clear. Some evidence suggests that prophylactic immune serum globulin may prevent some cases of NANB posttransfusion hepatitis,[92] but the dose and efficacy of the product are not well defined. Nor is the utility of immune globulin proven for postexposure prophylaxis. When there is a needle puncture or extensive mucous membrane exposure to tissues, serum or secretion from patients with NANB hepatitis, 5 ml (adult dose) of immune globulin or an equivalent pediatric dose (0.02 ml/kg) can be given. Otherwise, careful attention to hygiene may be all that is necessary.

Influenza[51]

Routine immunization against influenza is not recommended for normal children because of the vaccine's limited effectiveness and undesirable systemic reactions, particularly high fever in subjects under 3 years of age.[104,171] Children at particular risk (immunosuppressed patients, and those with asthma, diabetes mellitus, congenital or rheumatic heart disease, cystic fibrosis, chronic renal failure[84]), may benefit from yearly immunization with polyvalent killed influenza vaccine in a dose adjusted for children. Transient increased impairment in air flow (but not asthmatic attacks), requiring additional bronchodilator therapy, has been reported in asthmatic children receiving killed influenza vaccine. However, these same children were significantly protected against influenza-like illness during an epidemic.[13]

Vaccination may cause elevated serum concentrations of theophylline due to decreased hepatic metabolism.[57] This is rare, in our experience in children. The effect is thought to be due to interferon stimulation, which depresses hepatic cytochrome P-450 activity, so influenza vaccination should be performed cautiously in patients receiving drugs that are metabolized by the liver.[95]

Immunogenicity and reactogenicity were comparable to those of normals in children with renal disease.[96] Children with malignancies have a good immune response when therapy is suspended for 1 month and when peripheral white blood cell counts are higher than 1000/mm^3.[66] However, they are often unresponsive to primary or booster doses while receiving chemotherapy.[24] Since transplacentally acquired antibody has been correlated with protection of newborn and young infants,[137] vaccination of pregnant women should be considered during, or in advance of, serious influenza outbreaks.

One dose of vaccine may be sufficient for most patients[76] and is now recommended for primary and booster immunization.[27] The strains contained in such a vaccine will vary from year to year, according to the epidemiologic situation, especially with respect to the antigenic shift of the A2 strains; the vaccine should always contain a type B antigen. The 1983–1984 vaccine contains 15 μg each of the following antigens: A/Brazil/IV 78 (H1N1), A Philippines/2/82 (H3N2), and B/Singapore/222/79. Split-virus vaccine is preferred for children under 13 years. The dose is 0.25 ml for children under 13 years of age and 0.5 ml for those above this age. Simultaneous administration of influenza and pneumococcal vaccines is safe and effective.[47]

Influenza virus vaccines produced in recent years have been associated with few side effects. Three types of systemic reaction to influenza vaccine preparations have been described:

1. Fever, malaise, myalgia, and other symptoms starting 6–12 h after

vaccination and persisting 1–2 days. These responses to influenza vaccine are usually attributed to the influenza virus itself (even though it is inactivated) and constitute the majority of the side effects. They occur more frequently in children, especially with whole virus vaccine. A patient with immune thrombocytopenia has been reported to relapse after influenza vaccination.[90]

2. Immediate: presumably allergic responses, such as flare and wheal, or various respiratory signs of hypersensitivity. These reactions are exceedingly uncommon. They are probably a consequence of exquisite sensitivity to some vaccine component, most likely residual egg protein which is present in minute quantities (see Allergy above).
3. Guillain-Barrê Syndrome (GBS): an uncommon illness, which is usually self-limited and followed by complete recovery. However, 5–10% of persons with GBS have residual weakness and approximately 5% of cases are fatal.

Before 1976, no association of GBS with influenza vaccination had been recorded, but in that year an increased incidence was observed within 8 weeks following swine influenza vaccination. It was estimated to have occurred in 1976 in approximately ten per million persons vaccinated with swine influenza vaccine in North America, an incidence five to six times higher than that expected in nonvaccinated persons. Analysis of data in the United States from GBS surveillance during the 1978–1979 influenza season suggests that, in contrast with the 1976 situation, the risk of GBS in recipients of the 1978–1979 vaccine was not significantly higher than that in nonvaccinated persons.[77] Other neurologic side effects have also been reported but are rare.[54]

Measles

Live measles vaccines are immunogenic in more than 85% of recipients immunized at 12 months of age and in more than 95% immunized at 13 months or older.[86] Immunity has persisted for at least 20 years. Although the period of observation of further attenuated vaccines is shorter, protection appears the same despite a lower antibody titer. Causes of vaccine failure include the 5% nonresponders mentioned above, improper storage of vaccine, administration of vaccine with immunoglobulin, and vaccination at or under 1 year of age. It may be worthwhile to revaccinate the latter population, particularly those who were born before 1972 and are at increased risk of exposure.[172] Protection of infants under a year of age is best achieved by passive immunization; however, aerosolized measles vaccine may be immunogenic despite the presence of maternal antibody.[145] This approach is still experimental but its application may be relevant to populations with high rates of measles infection in the first year of life.

Inactivated measles vaccine afforded protection of limited duration; however, recipients have developed severe illness ("atypical measles") as long as 16 years after vaccination after exposure to natural measles.[60] This, or a modified disease, may rarely be seen after live, or after killed followed by live, vaccine is given.[39] Despite these reactions, children who have received killed vaccine in the past should receive live attenuated vaccine in an attempt to protect them against atypical and natural measles. Measles vaccine may be associated with hypersensitivity reactions at the site of injection in such patients. A fatal case of panniculitis has also been reported in a 14-year-old who received live measles vaccine 12 years after the killed product.[25]

Reimmunization is also recommended for children who either received measles vaccine before 1 year of age or who received vaccine with immune serum globulin. However, as many as 40% of children immunized before 10 months of age may not seroconvert after booster vaccination.[101] Measles vaccine is contraindicated in patients with tuberculosis unless they are receiving chemotherapy. Egg allergy is not usually a contraindication to measles, mumps, or rubella immunization. However, children with a history of severe hypersensitivity to egg white should be screened first with intracutaneous diluted measles vaccine. This can be done by a scratch or prick test with a 1:10 dilution of vaccine, followed by an intradermal test with a 1:100 dilution. If positive, the vaccine can be administered subcutaneously in slowly increasing increments of 0.05 ml, every 15–20 min.[71] Regardless of the skin test results, these patients should be observed for anaphylaxis for approximately 30 min after receiving vaccine.

Immunization with live vaccine within 48 h of known measles exposure will usually result in protection from the natural infection.[143] After 48 h, immune serum globulin is used (0.2 ml/kg) to prevent measles; the child should be immunized with live vaccine 12 weeks later.

Five to 15% of vaccinees may develop fever about a week after vaccination, with or without a mild rash. These effects rarely last more than 4 days. Encephalopathy and other neuropathies[36] may occur once for every million measles vaccine doses administered. However, this incidence, and the incidence of subacute sclerosing panencephalitis, are much lower after vaccination than after natural infection.[34]

Meningococcus: Groups A and C

Monovalent meningococcal A and C, and bivalent meningococcal A/C, vaccines are available. The protection is group-specific and no preparation is available for group B at this time. Immunogenicity is age-related, and young infants respond with low antibody titers that may not be protective. Serogroup A vaccine has been effective in field trials in children over 3 months of age and serogroup C vaccine in children over 2 years.

Meningococcal vaccines are recommended for closed populations such as institutions, nurseries, and military schools with endemic or epidemic infection. Monovalent vaccine can also be used to supplement antimicrobial prophylaxis in household contacts. Local discomfort and rare allergic reactions have been reported. The duration of immunity may be as short as 1 year with certain lots of vaccine.[163] Revaccination every 3 years is probably necessary in children under 6 years of age immunized with group A vaccine.[87] Vaccination during pregnancy does not induce tolerance in offspring.[108]

Mumps

Mumps vaccine is a live attenuated virus grown in chicken fibroblasts and is available alone or in combination with measles and/or rubella vaccines. Protective immunity has persisted through at least 12 years.[165] Adverse reactions are limited to local pain and erythema at the injection site and are rare. There is no clear evidence that mumps can be prevented by hyperimmune γ-globulin.[61] The skin test is not reliable in predicting susceptibility. Immunization with live vaccine on the day of exposure may not protect against clinical illness, but no harm has been demonstrated from this procedure.

Pertussis (see also DTP)

Pertussis vaccine is administered subcutaneously. Adverse reactions in children are common but mild, and include fever and local inflammation. Pertussis vaccine can be given together with influenza vaccine.

Pneumococcus[45]

Pneumococcal bacteremia, pneumonia, meningitis, and other invasive disease can be prevented by vaccination with a 23-valent preparation of pneumococcal capsular polysaccharide. It is indicated for children at high risk for pneumococcal infection (postsplenectomy, sickle-cell anemia, nephrotic syndrome,[56] and possibly for those with other hemoglobinopathies complicated by functional asplenia and immune deficiencies). Because of variable immune responses in these hosts, and vaccine failure,[120] it should be used as an adjunct to penicillin prophylaxis and careful patient surveillance.

The vaccine is poorly immunogenic in children under 2 years of age and in those with sickle-cell disease under 3 years,[127] and does not prevent pneumococcal rhinitis or sinusitis. Recent reports even question the efficacy of vaccination in children under 10 years of age.[22] Sickle-cell patients over 4 years of age respond poorly to types 6A and 19F.[85] If practical, the vaccine should be administered at least 2 weeks before splenectomy. Patients splenectomized for trauma or hemolytic anemia may have a relatively normal antibody response while those with functional asplenia or who have been splenectomized for Hodgkin's disease may not. The antibody response in Hodgkin's disease is significantly improved if vaccination is given before radiation and chemotherapy.[1] Radiation and chemotherapy may be more important causes of this poor response to vaccination than is splenectomy.[117] Candidates for renal transplantation should be immunized before surgery while undergoing hemodialysis.[102] Patients with steroid-responsive nephrotic syndrome respond better than steroid-resistant cases.[153]

Side effects are infrequent and mild. They consist of swelling and pain at the injection site; fever and severe swelling are rarely seen.[67] Thrombocytopenia has been noted in patients with a history of immune thrombocytopenia.[40] Simultaneous administration of pneumococcal and influenza vaccines is safe and effective.[47]

Poliovirus

Two preparations are available. The inactivated (killed, Salk, injectable) vaccine is usually recommended for primary vaccination of adults and for all vaccinations in health care workers and in patients (and their household contacts) for whom live virus vaccines are contraindicated, because excretion of live polio virus may present a risk to contacts, or for immunologic reasons (killed vaccine is available in the U.S. from Elkins-Sinn Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08802). If a household contact of an immunodeficient patient is immunized with oral poliovirus vaccine, close contact should be avoided for 1 month.[33] Since at present in the U.S. more deaths occur from live polio vaccine (about seven/year) than from the natural disease, use of the inactivated vaccine is being seriously reconsidered.[59] For the present, the live vaccine appears preferable because (1) it offers both intestinal and systemic immunity,[89] (2) it is simple to administer, and (3) it does not appear to require repeat administration into adulthood (antibody has persisted for at least 10 years).[146]

The risk of live vaccine-associated poliomyelitis in vaccinees is approximately one per three million doses.[33] The risk is increased in contacts and in adults. Evidence from experimental infection suggests gastrointestinal passage of virus increases its virulence. Because of this risk, some countries routinely use inactivated vaccine. However, this is given subcutaneously and may require booster doses every 5 years. Since one dose of oral vaccine will effectively offer durable immunity (8 years[141]) when given after a course of Salk vaccination,[107] some physicians use a killed, followed by live, schedule to decrease the risk to the vaccinee. However, this probably does not lower the risk of disease in contacts.[169] Adults should receive inactivated vaccine if not previously immunized. If the time available for immunization before travel is less than 4 weeks, use live vaccine.[33]

The primary series of polio vaccination consists of two or three doses, each separated by 8 weeks. It is advisable to administer an additional dose of vaccine containing all three serotypes of poliovirus to subjects fully immunized 5–6 years previously for travel to highly endemic areas.[12] This will ensure protection to all three types of poliovirus. Multiple doses are suggested in early childhood to ensure maximum "take" rates. Breast feeding should be interrupted only in *newborns* receiving live oral polio vaccine;[46,132] a 6-h period before and after ingestion of the vaccine is sufficient. Attenuated Sabin strains are available in human or monkey tissue culture cells.[110]

Rabies (Tables 1–3, 1–4)

Since elimination of rabies virus at the site of infection by chemical or physical means is the most effective mechanism of protection, immediate washing and flushing with soap and water,[3] detergent, or water alone is imperative. Then apply either 40–70% alcohol, or tincture or aqueous solutions of iodine.

If the bite is due to a rabid animal, vaccinate with rabies vaccine and administer human rabies immunoglobulin (RIG). The dose is 20 IU/kg. One-half of this dose is given by careful instillation into the depth of the wound and by infiltration around the wound; the rest is given intramuscularly. Postpone suturing of the wound. If RIG was not administered when vaccination was begun, it can be given up to the eighth day after the first dose of vaccine.[125] Persons who have been previously immunized with rabies vaccine and have a documented adequate rabies antibody titer should receive only vaccine. Where indicated, institute antitetanus procedures and administer antibiotics to control infections other than rabies.

Human Diploid Cell Rabies Vaccine (HDCV) is now available and is the prevention of choice together with RIG.[4] One milliliter of this vaccine is given subcutaneously on days 0, 3, 7, 14, and 28. Results to date have shown that antibody persists for 4 years.[53] Doses as small as 0.1 ml intradermally have also produced good antibody responses.[14] Local reactions (pain, erythema, swelling, itch) occur in about 25% of vaccinees; mild systemic reactions (headache, nausea, abdominal pain, muscle aches, dizziness) occur in about 20%. One case of Guillain-Barré syndrome[19] and one of transient neuroparalysis[15] have been reported. For dosage and indications of serum and vaccine see Tables 1–2, 1–3.

Rubella[118]

Although only 8–20% of women reach childbearing age without acquiring immunity, infection in these susceptible individuals during pregnancy carries a high risk of fetal abnormalities. Present immunization programs are designed to protect these women (1) directly, (2) by serologic testing and vaccination of adolescent females, or (3) indirectly, by immunizing large numbers of children. It is hoped that immunized girls will maintain immunity into adulthood, although this has not been proven. More than 95% of vaccinees will develop antibody against rubella[43] but failure rates up to 36% have been reported.[8] Antibody levels are lower but persist for at least 10 years in over 97% of vaccinees. The rate of decline is similar to that following natural infection;[72] persistence of antibody to 16 years has been reported in England.[126] High primary and secondary failure rates reemphasize the importance of preconceptional serologic testing in females followed by appropriate immunization. Despite the fact that vaccinees shed virus from the upper respiratory tract 7–22 days after vaccination,[48] transmission of vaccine virus to susceptible individuals has not been demonstrated.[58,91]

The new vaccine strain RA 27/3 is preferable, as it is grown in human diploid cells and reinfection is rare with its use.[37] Introduced recently into clinical use, this vaccine stimulates local IgA antibody production in the nasopharynx and probably offers better protection than previous products.[9]

Vaccinees may experience mild fever, rubella-like rash, lymphadenopathy, and transient arthralgia or arthritis up to 8 weeks after immunization.[168] Attenuated rubella virus has been recovered from the knee joint in arthritis secondary to immunization.[167] Arthropathy is rare in young children[168] but may be recurrent.[159] Vasculitis and myositis have also been reported.[68] Neuropathy is rare but may recur up to 2½ years after vaccination.[147]

The vaccine is contraindicated in females who may be pregnant at the time of administration or who may become pregnant during the subsequent 3 months. Rubella vaccine-like virus has been isolated from fetal tissues[30]; however, congenital rubella syndrome has not been recorded among 83 newborns born to vaccinated susceptible mothers.[35] The risk of fetal infection after intragestational immunization seems remote with RA 27/3 strain.[17] Serologic conversion in vaccinees without evidence of disease has occurred after exposure to natural rubella; however, viremia and teratogenic effects have not been demonstrated.

Smallpox

Vaccination against smallpox is *no longer recommended* (except for personnel working with variola virus). Those continually at risk should receive vaccination at 3-year intervals. The last case of smallpox in the world was detected in October 1977. The continued use of vaccinia for the treatment of a variety of unrelated conditions and for travel is unwarranted and has caused progressive disease in the unsuspecting victim.[88]

TABLE 1–3. Active Immunization (Live and Killed Vaccines)

Occasionally employed vaccines

Disease	*Product*	*Live Agent*	*Killed or Toxoid*	*Dosage and Route*	*Hazards*
Cholera	Bacterial suspension[49,122,151]		X	2 doses at least 1 week apart SC or IM no more than 2 months before departure for endemic area 6 months–5 years: 0.1, 0.3 ml 5–10 years: 0.3, 0.5 ml > 10 years: 0.5, 1.0 ml Booster q 6 months	Severe reactions rare. Not recommended < 6 months of age. Seizures may occur in a high percentage of children with neurologic conditions. Limited effectiveness
Plague[78]	Bacterial preparation inactivated by formaldehyde		X	3 doses—1 and 2 four weeks apart, dose 3 6 months after first Boosters with continued exposure. < 1 year: 0.2, 0.04, 0.04 ml 1–4 years: 0.4, 0.08, 0.08 ml 5–10 years: 0.6, 0.12, 0.12 ml > 11 years: 1.0, 0.2, 0.2 ml	Severe local reactions, fever, chills. Limited indications for those contacting wild rodents or rabbits in endemic regions or laboratories working with plague. Contraindicated in subjects allergic to beef protein, or phenol, or those with history of severe reaction to prior vaccination. Degree of protection unsure, hence tetracycline or chloramphenicol should be given × 7 days to individuals heavily ex-

					posed to *Y. pestis*, regardless of vaccination status.
Rabies	Postexposure: Human Diploid Cell Rabies Vaccine		X	1 ml IM on days 0, 3, 7, 14, and 28 days after exposure.	Erythema and swelling at injection site in 25%
	Preexposure: Human Diploid Cell Rabies Vaccine		X	1 ml IM or 0.1 ml ID on days 0, 7, and 21. Boost with same dose q 2 years	
Typhoid			X	< 10 years: 0.25 ml SC per each of 2 doses 4 weeks apart: booster q 3 years. > 10 years—0.5 ml SC 4 weeks apart; booster q 3 years	0.1 ml ID may be used with less local and febrile reactions.[79] Not used < 2 or > 45 years. Paratyphoid vaccine is not recommended.
Typhus	Formaldehyde inactivated *Rickettsia prowazeki* in embryonated eggs.		X	2 SC doses 4 weeks or more apart. Booster SC q 6–12 months. See product monograph for dose.	Contraindicated in children allergic to egg. Indications for vaccine are rare.
Yellow fever	Chick embryo grown virus. 17D vaccine has lowest reaction rate.	X		0.5 ml > 6 months of age. Booster recommended q 10 years; however, recent study shows persistence of antibody for > 30 years after single vaccination[133]	Mild, febrile reactions, usually about 7th day. Contraindicated in egg allergic children and those with altered immune states. Rarely, neurologic reactions include meningitis, encephalitis, polyneuropathy, Guillain-Barré. Allergic reactions include urticaria, wheezing, angioneurotic edema, or anaphylaxis.
	Mouse brain vaccine contraindicated in children				

TABLE 1–4. Specific Systemic Treatment for Rabies

	Status of Biting Animal:		
Nature of Exposure	*At Time of Exposure*	*During 10 Days*[a]	*Recommended Treatment*
1. Contact but no lesions; indirect contact; no contact	Rabid	—	None
2. Licks of the skin; scratches or abrasions; minor bites (covered areas of arms, trunk and legs)	(a) Suspected as rabid[a]	Healthy	Start vaccine plus RIG. Stop treatment if animal remains healthy for 10 days.[a,c]
		Rabid	Complete the course of vaccine
	(b) Rabid; wild animal[d] or animal unavailable for observation		RIG + vaccine
3. Licks of mucosa; major bites (multiple or on face, head, finger or neck)	Suspected[b] as rabid domestic or wild[d] animal, or animal unavailable for observation		RIG + vaccine Stop treatment if animal remains healthy for 10 days.[a,c]

[a] Observation period in this chart applies only to dogs and cats.

[b] All unprovoked bites in endemic areas should be considered suspect unless proved negative by laboratory examination (brain FA)

[c] or if the brain is found negative by FA examination.

[d] In general, exposure to rodents (except bats) and rabbits seldom, if ever, requires specific antirabies treatment.

Tetanus (see also DTP)

Hypersensitivity reactions to tetanus toxoid are associated with high levels of circulating antibody.[52,129] Most individuals who have received an initial series of three or four injections have protective levels of circulating antitoxin 10–12 years later.[129] Therefore, limit tetanus toxoid boosters to: (1) patients for whom more than 10 years have elapsed since the last booster; (2) patients with wounds where more than 5 years have elapsed since the last booster (these recommendations may not be applicable in developing countries unless the duration of immunity is similar to the above).[113] [*Note*: Subjects with a history of reaction to tetanus toxoid should not receive a booster dose more frequently than every 10 years;[99] and (3) cases where the immunization history is uncertain or the patient has never been immunized. In the latter case, tetanus toxoid cannot be relied upon to protect the patients since it takes 2 weeks for protective levels of antibody to develop. Other measures, such as care of the wound and administration of human tetanus immune globulin and penicillin, should constitute the primary means of preventing tetanus. A subsequent full course of active immunization is necessary. Single-dose vaccination may be preferable in developing countries where partial immunity is acquired, probably as a result of clostridial colonization of the bowel.[44] Adult immunization boosters need to be stressed. Adsorbed tetanus toxoid is recommended because of higher and more prolonged antibody titers.[151] Only fluid toxoid should be used intradermally.

Combined Vaccines

Mixed vaccines containing live measles, mumps, and rubella virus (MMR) are available and are effective without increased side effects or loss of immunity.[97] Persistence of immunity has been comparable to monovalent vaccines at 10 years' followup after MMR and mumps-rubella, 9 years after measles-rubella, and 7 years after measles-mumps.[166] Thrombocytopenia has been reported with MMR.[150]

Simultaneous administration of killed and/or live vaccines without loss of antibody response or increase in toxicity is also possible for poliovirus, smallpox, yellow fever, cholera, typhoid, and plague. When possible, vaccines that commonly cause side effects (e.g., typhoid, plague, cholera) should be given at separate times. A minimum of 1 month should be allowed between doses when these vaccines are administered separately. Immune globulin should not be given for 3 months before, or at least 2 weeks after, live vaccines. Influenza and pneumococcal vaccine can be administered simultaneously.[47]

Mixed Bacterial Vaccines and "Cold Shots"

There is no supportive clinical evidence for the use of *B. catarrhalis*, respiratory, and other mixed bacterial or viral vaccines for the prevention of respiratory infections,[109] and these are not recommended. Efforts to demonstrate interferon production induced by such vaccines in humans have failed,[83] as have efforts to demonstrate efficacy in preventing respiratory infections or in decreasing the incidence or severity of asthma attacks.[93,144]

Experimental Immunizations (Not Available Commercially)

Adenovirus. Although oncogenic effects in animals have been demonstrated, studies have shown benefits of live attenuated adenovirus vaccination in army recruits in the USA.[149,160]

Caries. Efforts to prevent human dental caries are still experimental. Results indicate that specific salivary IgA antibodies reduce plaque and *Streptococcus mutans*-induced caries in rats,[114] and a purified protein antigen has been 70% effective in monkeys.[98]

Cytomegalovirus. Live human cytomegalovirus has been given to renal transplant patients in preliminary trials. No latency developed but protection was poor.[63]

Haemophilus influenzae b. Capsular polysaccharide vaccine has been developed for use in children but is poorly immunogenic in children under 2 years of age.[139,152]

Mycoplasma pneumoniae. Temperature-sensitive mutants have been immunogenic in animal experiments.[154] Inactivated vaccine is ineffective in children,[55] but 87% and 66% effective in adults against bronchitis and pneumonia, respectively.[119]

Pseudomonas aeruginosa.[130] An experimental lipopolysaccharide vaccine was most effective in the prophylaxis of Pseudomonas infections in severe burns, but resulted in limited reduction in fatal Pseudomonas infections in cancer patients. As expected, there was a high incidence of painful local reactions, as well as fever, malaise, and myalgia.[173]The vaccine was immunogenic, but ineffective in patients with cystic fibrosis.

Varicella. A live varicella vaccine (Oka strain) prevented chicken pox in exposed household contacts immunized within 3 days following exposure.[5] The vaccine also has been safely and effectively employed in children receiving steroid therapy and in leukemics in remission; the duration of immunity has been 2 years thus far.[6,80] Concerns about the long-term effects of this vaccine include latency, oncogenicity, and alteration in the age of the susceptible population.

Varicella-zoster immune serum globulin should be used to prevent varicella in high-risk patients (see Table 1-2). Pooled human immune serum globulin may not contain sufficient varicella antibody for this purpose.[81]

***Typhoid*: Oral Vaccine.** A live attenuated (epimerase-deficient) strain of *S. typhi* (Ty21a) has protected 87–100% of vaccinees in two trials.[170] Further, no side effects were noted, and reversion to virulence did not occur.[164] Some vaccine failures have been reported, however, which cautions against the assumption that vaccine efficacy will be similar in all populations.[73]

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2

Antimicrobial Therapy

Antimicrobial therapy is a difficult subject for textbooks because of the rapid rate of development of agents and information about indications, pharmacokinetics, efficacy, and toxicity. Nevertheless, the practice of pediatrics, especially with respect to infectious diseases, would be paralyzed without the availability of these therapeutic agents, and the principles of their use and abuse remain somewhat constant.

Principles

Several important decisions are necessary for the appropriate implementation of antibiotic therapy. These include the choices of drug, dose, duration, route, and avoidance of toxicity. Even before this, however, one must examine the decision to treat. So much antibiotic prescription is inappropriate (e.g., in situations where the most likely cause of infection is viral, for fever without specified cause, prophylaxis, and/or for suspicion of infection) that this deserves some comment. The decision to use antimicrobials should be made with much thought. A specific diagnosis should be considered and, therefore, a specific etiology used to justify the choice of drug. Implicit in such a decision are the epidemiologic, historical, and clinical features suggesting the diagnosis and the laboratory procedures (both nonspecific and microbiologic) that will identify the cause and assess the appropriateness of specific antimicrobial choices. Some of these laboratory guidelines are defined in Table 2–1. These guidelines can also be applied to infections due to fungi, viruses, chlamydia, and certain other microorganisms.

TABLE 2-1. Definitions of Laboratory Guidelines to Antimicrobial Activity

MIC:	Minimum inhibitory concentration; the lowest concentration of drug able to inhibit the multiplication of a certain population of bacteria
MBC:	Minimum bactericidal concentration; the lowest concentration of drug able to kill a certain population of bacteria
Sensitive:	A bacterium is considered sensitive if drug concentrations expected to inhibit or kill it are anticipated in the blood and at the site of infection.
Resistant:	A bacterium is considered resistant if drug concentrations in blood and at the site of infection are below that required for inhibition or killing.
Tolerant:	A bacterium is considered tolerant if more than eight times the MIC of a conventionally bactericidal drug is required for killing.
SIP:	Serum inhibitory power; the highest dilution of serum that is capable of inhibiting the multiplication of a specific bacterial population
SKP:	Serum killing power; the highest dilution of serum that is capable of killing a specific bacterial population

Drug Choice

Initially drug choice should include one or more agents effective against the common causes of the specific condition. In general, the more immunocompromised the host, the more important it becomes to use bactericidal drugs and synergistic combinations, and to achieve bactericidal concentrations of antimicrobial at the site of infection. The initial regimen should be adjusted, as soon as microbiologic data are available, to as narrow a spectrum of antibiotics as possible.[518] Side effects due to superinfection are often dose-related, as are diarrhea due to other mechanisms, leukopenia, etc. These seldom occur within the first few days of antimicrobial therapy. Reduction in the spectrum of antibiotics and reasonable adjustments in doses may avoid such problems in many cases.

Drug choices should also include consideration of the pharmacokinetics of that agent.[113] Thus the site of infection, host characteristics, and mechanisms of metabolism and excretion need to be considered. For example, patients with liver disease may metabolize chloramphenicol aberrantly and those with kidney disease may need adjustments in β-lactam and aminoglycoside antibiotics. Drug interactions, host allergies, and electrolyte and other substances contained in the drugs need to be considered. The sodium and potassium contents of penicillins are examples of the latter. Hypersensitivity may be a response to the antibiotic or other component, such as procaine in some types of penicillin.[161]

Dose/Frequency

Antimicrobial doses are usually derived from pharmacokinetic data in healthy adult human volunteers after appropriate animal studies.[13,37] Often these require modification after experience is acquired with ill subjects of various ages, underlying conditions, and renal or hepatic abnormalities.

Doses are selected that promise therapeutic efficacy without toxicity. Therapeutic efficacy is estimated from in vitro antibacterial activities, often verified in experimental animal infections.[468] Particular attention to individualization of doses is required for drugs with narrow therapeutic/toxic ratios (e.g., aminoglycosides, chloramphenicol) and in patients with abnormal renal function. Similarly, the location of the infection and the status of the host may require dosage changes. For example, high doses are usually indicated for the treatment of meningitis and infections in immunosuppressed hosts.

Dosage schedules are also arbitrarily derived from pharmacokinetic data and past experience. Recent advances in knowledge of microbe-antimicrobe interactions have permitted us to prolong dose intervals in many cases and to shorten durations of therapy as well.[366] For instance, twice daily penicillin, erythromycin, or cephalosporin administration may be adequate for treating otitis media, pharyngitis, and sinusitis in normal hosts.

Route

The route of administration of the drug should be determined by several considerations. Foremost are pharmacokinetic data. Again the site of infection and host characteristics are important. Although some bacteria are tolerant to the bactericidal effect of penicillins, this tolerance can usually be overcome by using higher doses, by using combinations of drugs, or by taking advantage of host mechanisms for concentrating drugs at the site of infection. For example, in urinary tract infections high concentrations of antibiotic can often be readily achieved even after oral administration. In some circumstances, this is a limiting factor, e.g., in the treatment of meningitis, where it is difficult to achieve high concentrations of aminoglycosides and penicillins within the cerebrospinal fluid (CSF).

The intravenous route is the most rapid and efficient way to deliver most drugs to the blood and subsequently to other compartments. This is not true for chloramphenicol, which requires hydrolysis to the active form, and is most bioavailable by the oral route. In this case, hydrolysis takes place more efficiently in the gastrointestinal tract than in the blood. The vomiting or comatose patient, and patients who for other reasons

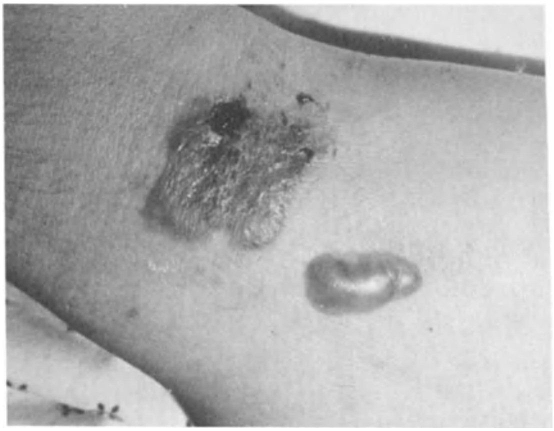

Figure 2–1. Bullous reaction due to acyclovir extravasation into subcutaneous tissue.

are unable to take drugs orally, obviously require therapy by the parenteral route. Occasionally, extravasation of antimicrobials can cause bullae, as in the case of acyclovir (Fig. 2–1), or tissue necrosis (Fig. 2–2).

Intramuscular antimicrobials have their place, but this is a restricted one in pediatrics. Where careful education and written and verbal communication can be used effectively to promote compliance with oral therapy, that route is certainly preferred over intramuscular administration.[441] Use of benzathine penicillin for the treatment of streptococcal pharyngitis or prophylaxis of rheumatic fever is effective, albeit painful. Pain is experienced by all, and long-term complications, such as quadriceps injury[294] and transverse myelitis,[511] in some. Almost half of the

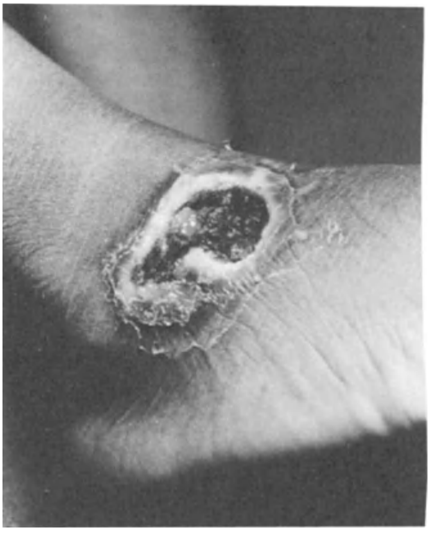

Figure 2–2. Tissue necrosis associated with infiltration of intravenous fluid containing ampicillin and chloramphenicol in a patient with meningitis.

children have severe pain at the site of injection and a third limp for a short period of time after such an injection. This encounter surely does not endear the health care provider to the patient! Other uses of intramuscular drugs include treatment of selected cases of venereal disease, and of patients who are vomiting or cannot otherwise tolerate oral medication. Certain drugs, such as chloramphenicol, should not be used intramuscularly because of poor hydrolysis and erratic delivery to the bloodstream. Similarly, patients in shock or with peripheral circulatory impairment, and those with thrombocytopenia and other bleeding diatheses, should not receive intramuscular medication.

The oral route is very efficient for some drugs, such as chloramphenicol, rifampin, and metronidazole; moderately efficient for others, such as amoxicillin, bacampicillin, and cyclacillin; and poor for some, such as penicillin G, cefaclor, cephalexin, and cephradine. The absorption and kinetics of antimicrobials are influenced by diet and nutritional status.[413] Nevertheless, even poorly absorbed drugs can easily reach concentrations sufficient to treat upper respiratory infections (e.g., streptococcal pharyngitis), urinary tract infections, and selected invasive infections.

Therapeutic Monitors

Whatever the route and drug choices made, some monitoring is usually needed. Clinical observation is usually adequate. Thus a clinical response is expected within 48 h in patients with otitis media, pneumonia, and wound infections. In other situations, some laboratory monitors may be indicated such as gram stain examination of a wound exudate, urinalysis, white blood cell count, or erythrocyte sedimentation rate. Bacteriologic monitors should be used in most serious invasive bacterial infections. Hence, followup urine, blood, and CSF cultures are recommended. The total information provided by clinical, inflammatory, microbiologic, and nonspecific laboratory features of the infectious process should be used to guide therapeutic decisions (Table 2–2). Often, busy, hospital-based training programs fail to emphasize the rewards and instructive value of patient followup.

Specific monitors of therapy include antimicrobial assays in various body fluids and/or the effects of these antibiotics in these fluids. In the former case, antimicrobial assays can be used to measure the concentrations of drug accurately to predict efficacy and/or avoid toxicity. Thus a comparison of the achieved drug concentration can be made with the minimum inhibitory or bactericidal concentrations of antimicrobial against the infecting bacteria, and dosage adjustments made. Similarly, toxic concentrations of aminoglycosides at peak and trough times should be avoided (Table 2–3). Antimicrobial assays are the method of choice for following patients with abnormal renal or hepatic function when the

TABLE 2–2. Therapeutic Monitors: Clues to Appropriate Antimicrobial Therapy

Clinical
- Fever reduction
- Well-being/cessation of rigors, nausea, vomiting, diarrhea, etc.
- Improvement in function (e.g., bone and joint infections)

Inflammatory (localized lesions)
- Decreased warmth, redness, swelling, tenderness
- Decreased drainage, sputum production, etc.
- Decreased neutrophil concentration in exudate, urine, CSF (increased glucose and decreased protein in CSF also)

Microbiologic
- Reduction or eradication of infecting pathogen

Nonspecific
- Return of erythrocyte sedimentation rate to normal
- Return of peripheral white blood cell count to normal
- Reduction in C-reactive protein concentration

antibiotics they are receiving are metabolized and/or excreted via these organs. Assays are also indicated in patients receiving drugs that may compete for pathways of metabolism (e.g., dilantin and chloramphenicol) or inactivate each other (e.g., ticarcillin and tobramycin).

The inhibitory and killing powers of antimicrobials in body fluids allow a physiologic estimate of the action of these drugs in the patient.[469] This can be measured in the patient's serum, urine, CSF, wound exudate, etc. For example, inactivation of aminoglycosides, penicillins, and cephalo-

TABLE 2–3. Interpretation of Antibiotic Concentration and Activity in Serum

	Therapeutic Range (μg/ml)	*Toxic Concentration Peak/Trough (μg/ml)*
Aminoglycosides		
Gentamicin	4–10	> 10/> 2
Tobramycin	4–10	> 10/> 2
Netilmicin	4–10	> 10/> 2
Amikacin	15–25	> 40/> 10
Kanamycin	15–25	> 30/> 5
Chloramphenicol	10–20	> 25/?
Flucytosine	50–100	> 100/?
Others		
Serum bactericidal activity	> 1/8	?
Serum peak drug concentration	4 × MIC 4 × MBC	

sporins in pus has been demonstrated.[59] Many clinicians prefer to use monitor of antibiotic activity for controlling the administration of drugs by the oral route for complicated infections. For example, a serum killing power of at least 1/8 has been effective as a guide in the treatment of bone and joint infections in children.[232] Qualitative compliance assays are also useful.[284]

Duration of Therapy

The duration of antibiotic therapy is determined by many considerations including the state of the host, etiology, and clinical course of the specific infection. In general, the more compromised the host (newborns, leukemics, transplant patients) and the more propensity the pathogen has for recurrence (group B Streptococcus, Brucella, Mycobacteria), the longer the duration of therapy. Conversely, shorter durations of therapy are more likely to be effective when rapid sterilization and clinical and laboratory improvement are noted. Use of drainage or surgical debridement may also allow reduction in the duration of antibiotic therapy. Rules of thumb to guide durations are as follows. In normal hosts, localized infections can be treated for 48–72 h after marked clinical improvement or resolution of some of the inflammatory findings. This is particularly useful in abscesses that have been drained, in wound infections, and in infections of the lower urinary tract. More invasive, systemic infections (bacteremia, subcutaneous tissue infections, pneumonia) should be treated for a minimum of 7 days after such events occur and eradication of the pathogen is demonstrated. In immunocompromised patients, at least 2 weeks of therapy after sterilization and marked improvement of signs and symptoms of infection is indicated. Therapy of 3 weeks or longer is indicated in certain situations, including neonatal meningitis, osteomyelitis, and nocardiosis. Exceptionally, such as in tuberculous infection, durations of therapy of at least 6 months are required. Remember, these are arbitrary guidelines, and individualization of regimens is often indicated.

Host Factors

Various conditions of the host may determine antimicrobial disposition.[253] Hepatic and renal impairment will obviously influence antimicrobials metabolized and/or excreted by these organs; however, thyroid (e.g., hypothyroidism) and systemic disease (e.g., exocrine gland dysfunction or its therapy, as in cystic fibrosis) may also influence drug handling. Systemic factors, such as fever, neutropenia, burns, and malignancy; and local factors, such as pH, inflammation, and pus, may also affect drug action.[253]

Mechanisms of Action

Some of the mechanisms of action of various antimicrobials are outlined in Table 2–4. Molecular events are not considered in detail, but summarized by anatomic location (in bacteria) or by metabolic pathway.[175] An understanding of these mechanisms is important to avoid certain pitfalls. For example, use of a cell wall inhibitor is of no value in the treatment of infections due to bacteria with defective walls, chlamydia, or Mycoplasma. Appreciation of the mechanism of action may also allow prediction of toxicity in some of these instances. Thus, patients with preexisting folate deficiency may require vitamin supplementation to avoid hematologic toxicity when taking trimethoprim and/or sulfamethoxazole.[14]

Combinations

Use of two antibiotics with similar mechanisms of action may also be nonproductive. In such situations, antagonism may occur by competition

TABLE 2–4. Mechanism of Antimicrobial Action

Aminoglycosides[a]	Interfere with protein synthesis
Macrolides[b]	
Tetracyclines	
Chloramphenicol	
Sulfonamides	Inhibit folate synthesis
Trimethoprim	
β-Lactams[c]	Enhance cell wall destruction
Bacitracin	
Vancomycin	
Peptides[d]	Damage cell membrane
Metronidazole	Impairs structure and function of microbial DNA
Ketoconazole	Impair synthesis of ergosterol, and therefore, cell membranes
Miconazole	
Amphotericin	Bind to sterols of cell membrane, leading to increased permeability and lysis of cell
Nystatin	
Flucytosine	Converted to 5-fluorodeoxyuridylic acid, which inhibits thymidilate synthetase and inhibits new DNA formation

[a] Gentamicin, tobramycin, amikacin, netilmicin, kanamycin, streptomycin

[b] Erythromycin, clindamycin, lincomycin (grouped for convenience as all are not strictly macrolides)

[c] Penicillins, cephalosporins, cephamycins, monobactams

[d] Colistin, polymyxin

for target sites, which is often an essential step before antimicrobial action can proceed. This is illustrated by the use of two penicillins together where competition for penicillin-binding proteins in the bacterial cell wall can reduce the net antibacterial effect. The degree of antagonism is generally small, and rarely clinically significant. Exceptions to this rule include the use of trimethoprim/sulfamethoxazole, where, despite the fact that they both affect folic acid metabolism, synergism rather than antagonism is usually noted.

More significantly, use of certain antibiotics that inhibit protein synthesis (e.g., tetracycline, chloramphenicol) may antagonize cell wall-active drugs (e.g., penicillin, cephalosporins).

Combinations are often used in the initial therapy of childhood bacterial infections and may be required for particularly resistant bacteria, such as *Pseudomonas aeruginosa,* or for infections where resistance to single drugs develops quickly (e.g., tuberculosis). Indications and risks of antimicrobial combinations are summarized in Table 2-5.

Antimicrobial Prophylaxis

Prophylactic uses of antimicrobials are listed in Table 2-6 and discussed in related chapters. The decision to use this approach (as in therapeutic use) rests on the clinician's assessment of potential risks and benefits. The major risks include drug toxicity and microbial resistance.[435a] Because of these risks, the burden of proof of efficacy falls on the physician using chemoprophylaxis.

Indications for antimicrobial prophylaxis may also include neutropenia and situations where specific exposures occur (e.g., pneumonic plague, accidental inoculations, pneumonic tularemia). Recurrent streptococcal

TABLE 2-5. Indications and Risks of Combination Antimicrobial Therapy

- Indications
  - Provide broad-spectrum activity
  - Treat mixed infections
  - Prevent emergence of resistance
  - Achieve an additive or synergistic effect
  - Reduce adverse dose-related effects of each drug
- Risks
  - Antagonism
  - Cumulative toxicity
  - Inactivation
  - Superinfection
  - Fluid overload
  - Expense

TABLE 2–6. Pediatric Antimicrobial Prophylaxis[a]

Illness	*Cause*	*Usual Prophylaxis*
Neonatal conjunctivitis	*N. gonorrhoeae* *N. gonorrhoeae/C. trachomatis*	Silver nitrate *or* erythromycin erythromycin
Rheumatic fever	*S. pyogenes* group A	Penicillin *or* sulfonamide
Endocarditis	Streptococci	Penicillin *or* erythromycin
Meningococcal infection	*N. meningitidis*	Rifampin *or* sulfisoxazole
Haemophilus infection	*H. influenzae* type b	Rifampin
Pertussis (under 1 year of age)	*B. pertussis*	Erythromycin
Urinary tract infection	*E. coli*, other enteric bacteria	Trimethoprim/sulfamethoxazole *or* nitrofurantion *or* sulfonamide
Gonorrhea	*N. gonorrhoeae*	Amoxicillin *or* penicillin *or* spectinomycin
Syphilis	*T. pallidum*	Penicillin
Otitis media	*S. pneumoniae, H. influenzae*	Sulfonamide *or* trimethoprim/sulfamethoxazole *or* amoxicillin
Pneumonia in immunocompromised patients	*Pneumocystis carinii*	Trimethoprim/sulfamethoxazole
Influenza	Influenza A	Amantadine
Tuberculosis	*M. tuberculosis*	Isoniazid
Malaria	Plasmodium	Chloroquine *or* pyrimethamine plus sulfadoxine

[a] See appropriate chapter for doses/discussion.

pharyngitis is rarely documented. When symptomatic pharyngitis is associated with streptococcal infection (verified culture of the organism *plus* a rise in antistreptococcal antibody titer), penicillin prophylaxis should be tried before tonsillectomy.[127] Often, there is another explanation, a not uncommon one being misidentification of group A Streptococcus.

Wounds that are deep, and difficult to debride adequately, may also require prophylactic antibiotics.[127] For example, prophylaxis for severe bite wounds might include penicillin and dicloxacillin.

Perioperative surgical prophylaxis is also commonly employed for operations where bacterial contamination is likely. Examples include shunt insertion for hydrocephalus (Chapter 9), cardiac prosthesis, appendicectomy (Chapter 6), and gastrointestinal surgery. In the latter circumstance, colonic surgery often carries a risk of postoperative anaerobic sepsis; hence cefoxitin or metronidazole are useful.[376] In almost all cases, the antimicrobial should be given intravenously prior to induction of anesthesia, and then repeated for only 2 or 3 doses.

Resistance

Mechanisms of resistance are many and some are not yet defined (Table 2-7). Several mechanisms may be represented in one bacterial population, or a plasmid may carry different genes coding for resistance against multiple antibiotics. These are particularly prevalent in closed units where antibiotic use and person-to-person spread influence selection of resistant bacteria.[260] However, community effects are also seen, as illustrated by typhoid bacilli resistant to chloramphenicol and ampicillin-resistant species of Shigella. Hence, consideration of this side effect of antibiotic usage both in hospitals and in the community is warranted. This pitfall can logically be extended to use in animal feeds and other community applications.[367] Occasionally, resistance may develop during treatment—another reason for bacteriologic monitoring.[473]

Toxicity

The toxicities of each drug are outlined under specific recommendations and will not be detailed here. Two side effects of antibiotics that are often forgotten include bacterial (or other microbial) resistance, as mentioned above, and sensitization of the host to allergic effects with subsequent doses. The origin of penicillin allergy in many adults can be traced to childhood experience with this class of drugs (Fig. 2-3). Although skin testing is useful to define some hypersensitivity states, such

TABLE 2–7. Mechanisms of Resistance

β-Lactamase	Plasmid-mediated Mutants
Inactivating enzymes (e.g., acetylase, phosphorylase)	
Decreased affinity of target (e.g., penicillin-binding protein). Loss (alteration) of target	
Decreased uptake of antibiotic (i.e., decreased permeability)	
Reduced ribosomal susceptibility	

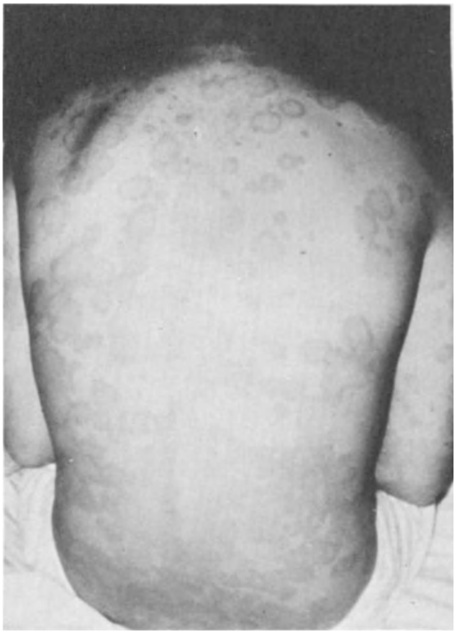

Figure 2-3. Cutaneous reaction associated with cloxacillin therapy.

as anaphylaxis and urticaria, there are no effective measures of allergy for certain antibiotics and for reactions such as erythema multiforme (Fig. 2-4).

Underuse of antibiotics may be equally problematic. Such is the situation where fear of toxicity or lack of familiarity with the drug may prevent the patient from receiving early and appropriate therapy. Where infections can progress extremely rapidly, e.g., in newborns, in immunocompromised patients, and occasionally in normals, this can be disastrous. In certain situations, such as fulminant meningococcemia, there may be no clinical clues that can be relied upon and no solution to the problem of making an accurate diagnosis and initiating early treatment of this condition.

One final note about toxicity is warranted. Often forgotten is the assurance that the organ of metabolism and/or excretion is normal. This can be checked by urinalysis and serum creatinine concentrations for most drugs excreted through the kidney. Equally important is assessment of liver function in patients receiving chloramphenicol, metronidazole, macrolides, doxycycline, and rifampin.[27] Baseline assessment of organ function that may be adversely affected by drugs (e.g., hearing and renal function in patients receiving aminoglycosides) is very important in patients in whom therapy is expected to be prolonged (i.e., longer than 7–10 days) or those with preexisting auditory or renal abnormalities.

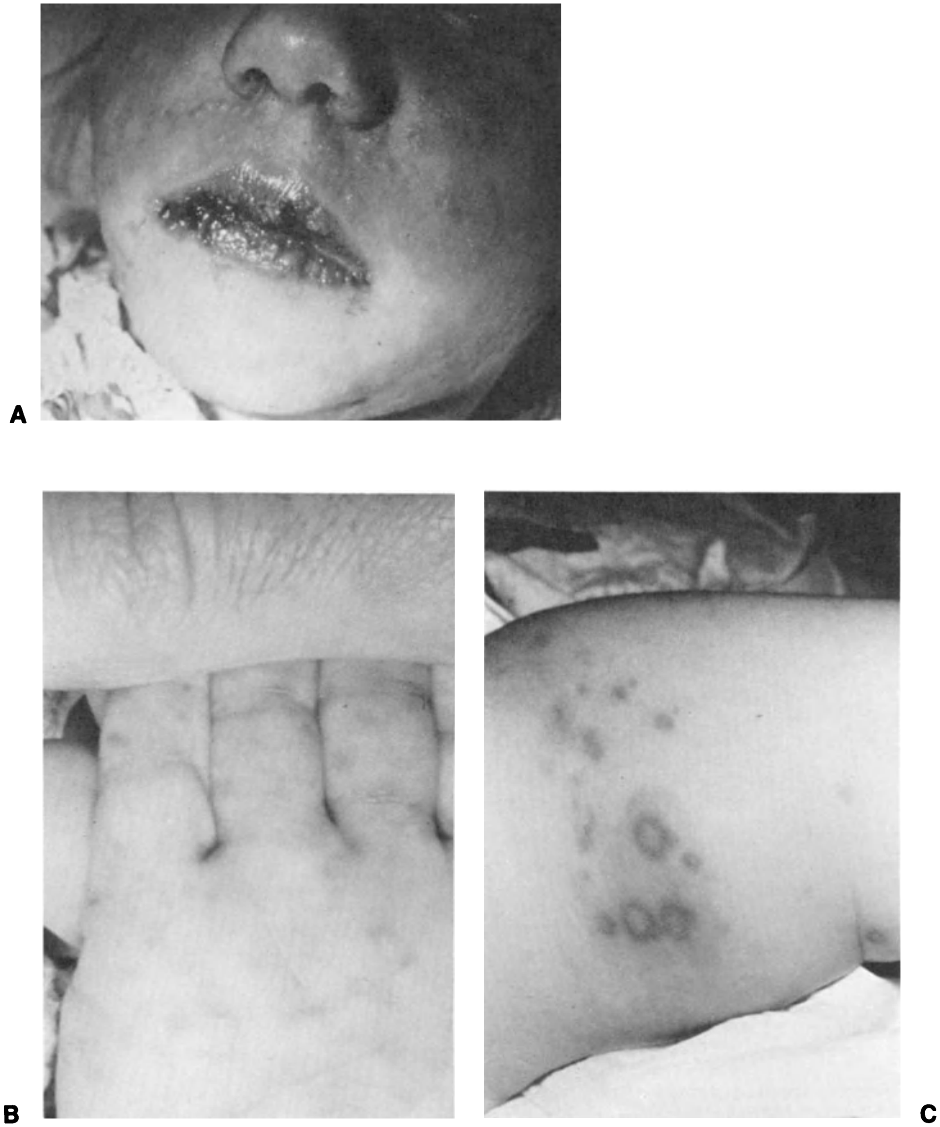

Figure 2–4. Three manifestations of antibiotic-associated erythema multiforme. **A**: Mucosal ulceration. **B**: Palmar rash. **C**: Hemorrhagic target lesions. For color reproduction of this figure see frontmatter.

Adherence to the aforementioned principles of diagnosis, antibacterial action, pharmacokinetics, and toxicity should provide a sound basis for antimicrobial therapeutic practice.

Specific Recommendations

I. Antibacterials*

Amikacin

Spectrum	Similar to that of kanamycin but active against many gentamicin-resistant species of Pseudomonas.
Dose	IV, IM: Initial loading dose of 10 mg/kg followed by 15 mg/kg/day divided q 12 h for the first week of life,[288] then 20 mg/kg/day (IV over ≥ 20 min) divided q 6 h.[80] Serum concentrations should be monitored. Excessive (> 40 peak or > 10 μg/ml trough) levels have been noted in some newborns, especially those ≤ 1000 g.[385] Patients with cystic fibrosis and children over 4 years of age may require as much as 60 mg/kg/day (420 mg/m^2/q 8 h) to maintain peak serum concentration of 15–25 μg/ml.[498] A dose of 7.5 mg/kg gives a mean peak serum concentration of 25 μg/ml and a mean peak ventricular CSF concentration of 6 μg/ml in children with ventriculitis.[533]
Toxicity	Similar to that of other aminoglycosides. Toxicity risk is high with concentrations > 40 μg/ml.[449]
Incompatibility	See Gentamicin. Serum concentrations are not affected by carbenicillin, even in renal failure.[44] However, cephalothin and moxalactam (based on in vitro studies) may inactivate amikacin.[206]
Comment	Pharmacology similar to that of kanamycin. Resistant to most gentamicin-inactivating enzymes. Monitor serum activity; *t1/2* may be reduced in burns.[536] Concentrations in bile are usually one-half of serum levels, and may accumulate with repeated doses.[40] May potentiate effects of botulinum toxin.[433]

Amoxicillin[359]

Spectrum	Similar to that of ampicillin except against Shigella species, which are often resistant in vivo to amoxicillin but respond to ampicillin.[358]

**Abbreviations used: SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase, LDH = lactic acid dehydrogenase, BUN = blood urea nitrogen*

Dose	Oral: 25–50 mg/kg/day divided q 6 h for urinary tract infections. 75–100 mg/kg/day for other infections, divided q 8 h. A dose of 15 mg/kg gives a mean peak serum concentration of 10 μg/ml and a mean peak middle ear fluid (chronic serous otitis media) of 1 μg/ml.
Toxicity	Same as that for ampicillin, but probably less diarrhea.
Comment	Same as ampicillin in most properties but generally absorbed more completely after oral administration. Sputum levels about 1/20 serum concentrations.[467]

Ampicillin

Spectrum	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, Listeria, and meningococci are sensitive. Approximately 10–25% of strains of *H. influenzae* are resistant to ampicillin (> 2 μg/ml) in many North American communities. Salmonella, Shigella, *E. coli*, Enterobacter, and Klebsiella resistances are increasing.
Dose	Oral: 50–150 mg/kg/day divided q 6 h. May be poorly absorbed in some patients with diarrhea.[355] IM, IV: 150–400 mg/kg/day divided q 4–6 h. For meningitis begin with at least 200 mg/kg/day divided q 4–6 h IV. Newborn:[213] 50–100 mg/kg/day divided q 12 h for first week of life, then 150–200 mg/kg/day q 6–8 h.
Incompatibility	Alkaline pH of IV solutions may inactivate if administered over 1 h.[531] Unstable in hyperalimentation solutions[129] and 5% G & W (use 0.9% NaCl). May reduce estrogen concentrations when given with oral contraceptives.[489]
Toxicity	Diarrhea;[31,32] colitis is rare;[218] drug fever; superinfections; hemolytic anemia. Although 10% of patients may develop a nonpruritic maculopapular erythematous rash, it is often transient despite continuation of therapy,[222] is not a contraindication to future penicillin therapy, and is not dose-related.[466] Urticaria incidence is 1%.[31] Perineal candidiasis may occur in infants (dose-related).[31] Interstitial nephritis is possible.[421]

Comment	Contains 1.7 mEq Na^+/500 mg of drug. May falsify urinary amino acid chromatogram.[462] Distributed well in body fluids of patients with hepatic cirrhosis.[261]

Azlocillin

Spectrum	*P. aeruginosa*: 75% sensitive to $\leq$ 12.5 μg/ml.[465] Anaerobes, including most *B. fragilis* are sensitive. Enterobacteriaceae are variably sensitive and there is some inoculum effect. Penicillin-producing species of Staphylococcus are resistant.
Dose	IV: 300–400 mg/kg/day, divided q 4 h (maximum 24 g).
Incompatibility	Antagonistic when combined with cefoxitin.
Toxicity	Allergic reactions (cross-allergenic with other penicillins); serum sickness-like symptoms;[338] IM too painful.
Comment	This is an acylureidopenicillin containing 2.2 mEq Na^+/g. Pseudomonas resistance has developed in some cystic fibrosis patients receiving azlocillin alone.[338]

Bacampicillin[317]

Spectrum	Same as that of ampicillin/amoxicillin.
Dose	Oral: 25 mg/kg/day, divided t.i.d. or b.i.d.
Toxicity	Same as that for ampicillin.
Comment	This is a semisynthetic hydrolyzable carbonate ester of ampicillin. It is completely hydrolyzed to ampicillin, its advantage being rapid and complete absorption. Indications are similar to those for amoxicillin.

Bacitracin

Spectrum	Gram-positive bacteria.
Dose	Topical: eye and skin, 500 units/ml.
Toxicity	Blood dyscrasias; rare allergy.[417]
Comment	May be absorbed significantly from large denuded areas and irrigation sites. 1 Unit = 18.2 μg.

Carbenicillin (also see Penicillins)

Spectrum	Gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa,* Proteus, Enterobacter, and *H. influenzae.* Meningococci, gono-

cocci, streptococci, and pneumococci are more susceptible to penicillin. *E. coli* and Salmonella species are more susceptible to ampicillin. Penicillinase-producing staphylococci, enterococci, many species of Serratia, and almost all species of Klebsiella are resistant.

Dose	Oral form (indanyl): 100 mg/kg/day divided q 4–6 h is useful for urinary tract infections due to enterobacter, pseudomonas, and indole-positive proteus species.[313,475] Serum concentrations too low for treatment of systemic infections. IV, IM: 100–200 mg/kg/day for proteus, and pseudomonas urinary tract infections. IV: 300–600 mg/kg/day divided q 2–4 h for other systemic infections. Newborn: 400 mg/kg/day divided q 6 h IV (serum concentration 50–200 μg/ml).[297,343] Except: ≤ 2000 g-100 mg/kg/day divided q 12 h to age 7 days.
Incompatibility	Should not be mixed with gentamicin, kanamycin, or colistin in syringe or IV infusion fluid.[411,525] Unstable in amino acid solutions.[83]
Toxicity	Reversible rise of SGOT. Hepatitis[520] may not be cross-reactive with ticarcillin.[158] Skin rash; convulsions; neuromuscular irritability; pain at site of IM injection; eosinophilia; granulocytopenia;[406] hemorrhage;[10] hemorrhagic cystitis.[337]
Comment	High doses required to achieve bactericidal blood levels for most organisms. Renal and urinary levels decreased in renal disease.[515] Resistance may develop when used alone.[285] For serious systemic gram-negative infections, combination with gentamicin may be synergistic,[114,384] may prevent emergence of resistance, and may allow for lower dosage of gentamicin in patients with renal failure. Each gram of carbenicillin contains 4.7 mEq Na^+.

Cephalosporins[335]

Approximately 15 cephalosporins are available; four are absorbed orally (cephalexin, cephradine, cefadroxil, and cefaclor). Properties shared by members of this group are: resistance to penicillinase, activity against many gram-positive (Staphylococcus, pneumococcus, Streptococcus other than enterococcus) and selected gram-negative bacteria. Cephradine and cephaloridine are least protein-bound (10–30%), while cefazolin is most (85%); most (except cefoperazone) are excreted by the kidneys and $t_{1/2}$s are short (½–2 h); penetration into the CSF and interior of the eye[15] is often poor but newer derivatives (cefuroxime and third-generation) are useful in the therapy of meningitis. The drugs cross the placenta and enter biliary, synovial, and pericardial fluids well; risk of allergic reaction in patients allergic to penicillin is estimated at 5–16%. Pseudomembranous colitis has been reported.[479] Antibacterial activity may be enhanced by mitomycin C but antagonized by bleomycin.[333]

Cefaclor

Spectrum	Less active against gram-positive bacteria including *S. aureus* (MIC range 1–100 μg/ml). Activity against *H. influenzae* is variable.[307]
Dose	Oral: 40–60 mg/kg/day (divided q 6–8 h). 10 mg/kg suspension gives a mean peak serum concentration of 10 μg/ml (0.5–4 μg/ml in middle ear fluid); peak is attained 45 min after suspension and 60 min after capsule.[456]
Toxicity	See other Cephalosporins. A serum-sickness reaction has been noted after repeated courses of cefaclor.
Comment	Absorption unaffected by milk.

Cefadroxil

Spectrum	Similar to those of cephalexin and cephradine.
Dose	Oral: 40 mg/kg/day divided q 12 h.
Toxicity	See other Cephalosporins and Cephalexin.
Comment	Longer half-life may permit q 12 h treatment for urinary tract infections.

Cefamandole

Spectrum	Same as that of cephalothin except less activity against some strains of *S. aureus* and more activity in vitro against *H. influenzae*; active against some enterobacteriaceae resistant to other cephalosporins. Some staphylococci may be relatively resistant.
Dose	IM, IV, 50–150 mg/kg/day divided q 4–6 h. A

	35 mg/kg dose gives a peak serum concentration of 100 μg/ml.
Incompatibility	Antabuse-like effect with alcohol (107).
Toxicity	Allergic skin rashes; drug fever; eosinophilia; same as that for other cephalosporins but not very nephrotoxic. Hypoprothrombinemia due to antibiotic-induced vitamin K deficiency.[423]
Comment	Specific disk required for susceptibility testing. Not recommended for systemic *H. influenzae* infections in infants, because meningitis can develop while the patient is on therapy.

Cefazolin[216]

Spectrum	A parenterally administered cephalosporin with certain pharmacological advantages over cephalothin and cephaloridine (higher and more sustained blood levels).[216]
Dose	50–100 mg/kg/day (divided q 8 h). IV, IM: 10 mg/kg gives peak serum concentrations of 35 μg/ml in children.[225]
Toxicity	See other Cephalosporins.
Comment	Inactivated more easily than other cephalosporins by penicillinase.[325] High bile concentrations except with cystic duct obstruction.[325,404] Poor CSF penetration.[23] Penetrates bone and synovial fluid well.[124] Half-life increases with renal failure;[94,258] eliminated by hemodialysis but not by peritoneal dialysis;[274] give dose (7–15 mg/kg) every 72 h in renal failure (creatinine clearance < 10 ml/min/1.73 m^2); repeat ½ dose after hemodialysis.[182]

Cefoperazone

Spectrum	Gram-positive and gram-negative aerobes and many anaerobes are sensitive. Active against group B streptococci and *Streptococcus pneumoniae.* Inactive against Listeria, enterococci, and some strains of *Bacteroides fragilis.*
Dose	Adult dose 1.5–4.0 g q 6–12 h IM or IV. Not yet approved for pediatric use.
Toxicity	Diarrhea (3%); skin rash (2%); thrombophlebitis (< 1%); nausea and vomiting, especially with alcohol ingestion. Can cause bleeding due to hypoprothrombinemia. See Cephalosporins.

Comment	Excreted in bile in high concentrations (elevated serum levels in hepatic failure); only 25% of drug excreted in urine.[220] Contains 1.5 mEq Na^+/g.

Cefotaxime

Spectrum	Gram-positive and gram-negative aerobes and many anaerobes are sensitive. Inactive against Listeria, enterococci, Pseudomonas, and Acinetobacter.
Dose	IV: 50–180 mg/kg/day, divided q 6 h. Newborns: 100 mg/kg/day, in first week of life, divided q 12 h. 150 mg/kg/day in second to fourth weeks of life, divided q 8 h.
Toxicity	See Cephalosporins.
Comment	Recently approved for use in children. Preliminary results indicate a potential role for treatment of serious invasive gram-negative sepsis and meningitis, including those due to *H. influenzae.*

Cefoxitin[348]

Spectrum	Gram-positive and negative bacteria usually susceptible (wide range) except *Pseudomonas aeruginosa, Enterobacter cloacae,* enterococci, and methicillin-resistant staphylococci. Good activity against anaerobes.
Dose	150 mg/kg/day divided q 6 h (max. 12 g); gives peak serum concentration of 80 μg/ml.[348]
Incompatibility	Can antagonize antibacterial activity of beta-lactam are susceptible antibiotics.
Toxicity	Thrombophlebitis with IV administration. Very painful IM. Allergic rash, eosinophilia. Nausea, vomiting, and diarrhea. Reversible leukopenia, neutropenia, and hemolytic anemia.[348] Positive direct Coombs test.
Comment	Transient elevations in SGOT, SGPT, LDH, alkaline phosphatase, BUN, creatinine. May give false-positive glucose reaction in urine tested with Clinitest®. High concentrations may falsely elevate serum and urine creatinine concentrations measured by the Jaffe reaction.[425] **Caution:** Patients have developed meningitis during cefoxitin therapy.[348] Pus and joint fluid concentrations usually 1/2–2/3 serum levels.[348]

Cephalexin[20]

Spectrum	Same as that for cephalothin and cephaloridine. Gram-positive cocci are sensitive, including penicillinase-producing staphylococci and group A streptococci;[289,396] enterococci are resistant. Active against gram-negative rods including some *E. coli,* Klebsiella, Salmonella, *Proteus mirabilis,* and most Enterobacter. Pseudomonas species are resistant.
Dose	Oral: 50–100 mg/kg/day divided q 6 h. Suspension absorbed more quickly (peak < 1 h) than capsule (peak 1–3 h); absorption unaffected by food in older children [483] but decreased by milk in infants.[299] A dose of 15 mg/kg gives a peak serum concentration of 20–25 μg/ml at 1/2 h in a fasting infant.[299]
Toxicity	Diarrhea and cramps; allergic skin rashes; eosinophilia, leukopenia; elevation of SGOT; fever; positive direct Coombs test; gastrointestinal and genitourinary superinfection (bacterial and yeast).
Comment	Main use should be in oral therapy of infections previously treated with a parenteral cephalosporin. Effective sputum concentrations (0.3–3.42 μg/ml) are reached but these levels decrease as inflammation subsides.[169] False-positive test for reducing substances in urine.

Cephaloridine[19,280]

Spectrum	Generally the same as that of cephalothin with the following exceptions: greater in vitro activity, less resistant to staphylococcal penicillinase, penetrates tissue fluids better than cephalothin, more nephrotoxic.
Dose	IM, IV: 50–100 mg/kg/day (not to exceed 4 g) divided q 6 h.
Incompatibility	Precipitate with heparin in NaCl and G & W. Concurrent ethacrynic acid or furosemide therapy may increase nephrotoxicity. Probenecid inhibits renal excretion.
Toxicity	Dose-related nephrotoxicity; eosinophilia; leukopenia (rare); thrombophlebitis (rare); pseudomembranous colitis.[479]
Comment	Less painful than cephalothin IM. May cause positive test for reducing substances in urine.

Cephalothin

Spectrum	Equivalent in vitro to penicillin against most gram-positive cocci *except* enterococcus. *H. influenzae* and clostridia are also relatively resistant. Active against penicillinase-producing staphylococci, most *E. coli,* and *Proteus mirabilis.* Ineffective against Pseudomonas, most Enterobacter species, nonmirabilis (indole-positive) Proteus, and many species of Klebsiella. Sensitivities should be determined before use for gram-negative infections.
Dose	Oral: **Not absorbed.** IV: 75–150 mg/kg/day divided q 4–6 h. Serum peak approximately 20 μg/ml after 25 mg/kg dose. Newborn: 50–100 mg/kg/day divided q 12 h in first week and q 8 h to age 4 weeks.
Incompatibility	Do not mix with polymyxin B, tetracycline, erythromycin, calcium chloride, or gluconate.
Toxicity	Severe pain IM; sterile abscesses; drug fever; positive direct Coombs; anemia; thrombocytopenia;[159] pancytopenia;[480] eosinophilia; thrombophlebitis;[197] rash; serum sickness with high doses and fast infusion rates.[430] Nephropathy is rare but may include acute renal failure.[67,432]
Comment	Particularly useful as a penicillin substitute in penicillin-sensitive persons. Anaphylaxis has been reported but is rare clinically, although the incidence of in vitro sensitivity to cephalothin is high in penicillin-sensitive persons.[466] In combination with kanamycin, may be beneficial in the treatment of selected staphylococcal infections[61] and may be synergistic in resistant *E. coli* infections. Cephapirin or cephradine are reasonable alternatives to cephalothin and may cause less phlebitis (11% vs 23% with cephalothin).[197] CNS penetration often inadequate especially with low CSF protein concentrations.[257] Good levels in bile.[401] Brown-black Clinitest® (no effect on glucose oxidase reaction). Elevates SGOT and alkaline phosphatase.[185] May falsely elevate creatinine concentration[403] measured by the Jaffe reaction. Pseudoproteinuria with trichloroacetic acid method.[11]

Cephradine

Spectrum	Similar to that of cephalexin.
Dose	Oral: 40–60 mg/kg/day divided q 6 h. May require up to 150 mg/kg/day for bone and joint infections.[232] Absorbed best in fasting subjects (e.g., mean peak serum concentration 21.3 μg/ml 30 min after 15 mg/kg/dose).[152] IM, IV: 50–100 mg/kg/day divided q 6 h.
Toxicity	Same as that of other cephalosporins.

Chloramphenicol

Spectrum	Bacteriostatic activity against Salmonella sp., *Bacteroides fragilis,* anaerobes, rickettsiae, and chlamydiae. Bactericidal against *H. influenzae.*
Dose	Oral, IV: 50–75 mg/kg/day divided q 6 h. IM: Should not be used as absorption is poor.[109] Intraventricular: ⅕–⅒ total daily dose (should use pure powder, as salt forms need to be hydrolyzed to be active). Newborns: 25 mg/kg/day for babies ≤ 14 days, in one daily dose. 50 mg/kg/day divided q 12 h for > 14 days old. Monitor serum concentrations.[43]
Incompatibility	Do not mix with polymyxin B, tetracycline, vancomycin, hydrocortisone, B-complex vitamins, alcohol (antabuse-like symptoms). May decrease liver metabolism of bilirubin, phenytoin, phenobarbital, and bishydroxycoumarin.[234,412] May increase effects of hypoglycemics.[309] Phenobarbital may increase metabolism by liver enzyme induction.[375]
Toxicity	Vasomotor collapse (gray syndrome) with serum levels ≥ 50 μg/ml.[243] Neutropenia with serum concentrations > 25 μg/ml. Cardiotoxicity (left ventricular dysfunction).[41] Aplastic anemia[503] and other hematopoietic toxicity even after topical use.[2] Hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Gastrointestinal symptoms; stomatitis; candida infections; allergy; hepatitis-pancytopenia syndrome.[70] Optic neuritis is rare. Neuropathies are rare. May inhibit humoral antibody responses.[412]
Comment	May be antagonistic when combined with gentamicin.[470] Good brain penetration.[236] Use should be accompanied by appropriate screening for

liver function and hematopoietic toxicity. May cause reversible loss of HL-A antigenicity.[33] If chloramphenicol is required for topical therapy of conjunctivitis, a 1% ointment applied every 4 h provides excellent drug concentrations in tear and aqueous humor.[173]

Clindamycin

Spectrum Approximately the same spectrum of activity as lincomycin and, to a somewhat lesser degree, erythromycin; main advantages over these agents are superior intestinal absorption (80–90% for clindamycin vs. 20–30% for lincomycin)[97,272] and efficacy in anaerobic infections.[29,126] Bacteriostatic against most anaerobic bacteria, especially *Bacteroides fragilis*;[532] most strains sensitive to ≤ 3.1 μg/ml.[30] Active against gram-positive bacteria including penicillinase-producing staphylococci.[301] *H. influenzae, N. gonorrheae, N. meningitidis, S. faecalis,* and gram-negative bacteria are resistant.[215] *Mycoplasma pneumoniae* sensitive in vitro[16] but clindamycin not effective in vivo.[447]

Dose Oral: 10–30 mg/kg/day divided q 6 h. 2–4 mg/kg PO gives mean peak serum concentrations of 1.2–2.4 μg/ml. Food reduces absorption.

IM, IV: 15–40 mg/kg/day[315] or 150 mg/m^2/day.[215] 5–7 mg/kg gives mean peak serum concentrations of 8–10 μg/ml.

Incompatibility Do not mix with vitamin B complex, aminophylline, ampicillin, calcium gluconate, magnesium sulfate, and phenytoin. IV preparation must be given in infusion, never undiluted. May cause neuromuscular blockade with curariform drugs.

Toxicity Rashes in up to 10%;[315] diarrhea and colitis in up to 20%;[471,482,497] possible rise in serum bilirubin, alkaline phosphatase, SGOT, and SGPT with parenteral (phosphate) form;[315] Stevens-Johnson syndrome;[315] thrombophlebitis with IV;[315] granulocytopenia and thrombocytopenia are rare.[315] IM painful and sterile abscesses reported.

Comment CSF and brain concentrations poor.[387] Bone, synovial fluid,[130] and wound concentrations 60–85% of serum levels.[39] Dose should be modified in patients with significant liver disease[519] and renal

	impairment (no clearance by peritoneal or hemodialysis).[278] May antagonize action of aminoglycosides.

Cloxacillin (see also Penicillins)

Spectrum	Penicillinase-producing staphylococci and streptococci are sensitive.
Dose	Oral: 50–100 mg/kg/day divided q 6 h, given 1–2 h before meals. Not dialyzed. No adjustment necessary in anuria.[350]
Toxicity	Similar to that of other penicillins. Hepatic dysfunction;[116] Neutropenia and hematuria.[460]
Comment	Penicillinase-resistant. Dicloxacillin is better absorbed.

Colistin[500]

Spectrum	*Pseudomonas aeruginosa*; other gram-negative bacteria are sensitive.
Dose	Oral, **Not absorbed**: 15–20 mg/kg/day divided q 6 h. IM, IV: 5–8 mg/kg/day divided q 6–8 h. Intrathecal. **Do not use**. Contains dibucaine (see Polymyxin).
Incompatibility	Nephrotoxic drugs, curariform drugs.
Toxicity	Proteinuria, cylinduria, hematuria, increased BUN (reversible); paresthesias, ataxia, drowsiness, confusion; fever; rash; pain at injection site; neuromuscular blockade, especially after intraperitoneal administration with myaesthenia gravis or in anesthetized patients.[389]
Comment	Gains access to CSF only when used in doses > 10 mg/kg/day. **Do not use in persons sensitive to "caine" type local anesthetics**. May be used orally for neomycin-resistant enteropathogenic *E. coli* infections.

Co-trimoxazole: See Trimethoprim/Sulfamethoxazole

Cyclacillin

Spectrum	Same as that of ampicillin but less active against *S. pneumoniae* and *H. influenzae.*
Dose	Oral: 50–100 mg/kg/day divided q 6 h. 25 mg/kg gives peak serum concentration of 25 μg/ml 30 min after dose; unaffected by food.[155]
Toxicity	Same as that for ampicillin. Diarrhea in 4%; rash in 2%.

Toxicity	Same as that for ampicillin. Diarrhea in 4%; rash in 2%.

Dicloxacillin (See also Penicillins)

Spectrum	Penicillinase-producing staphylococci are sensitive.
Dose	Oral: 50–100 mg/kg/day divided q 6 h. In bone and joint infections, begin with 100 mg/kg/day, and decrease if serum killing power indicates this is possible.
Toxicity	Gastrointestinal irritation which appears to be dose-related. May cause *C. difficile* colitis.[55]
Comment	Rapid renal clearance in cystic fibrosis patients (increase dose and/or frequency and monitor serum levels).[207]

Doxycycline: See Tetracyclines

Erythromycin

Spectrum	Gram-positive cocci including many penicillinase-producing staphylococci, clostridia, *Bordetella pertussis, C. diphtheriae,* rickettsia, and some Bacteroides are sensitive. Resistance of some group A streptococci and some pneumococci has been reported. As effective as tetracycline for symptomatic relief of *Mycoplasma pneumoniae* infections.[448] Chlamydia are sensitive.
Dose	Oral: 30–50 mg/kg/day divided q 6 h. IV: 40–70 mg/kg/day divided q 6 h, given over 20–60 min period. Newborn and infants < 4 months, oral, 20–40 mg/kg/day divided 8–12 h.[378]
Incompatibility	Lincomycin. Acid pH inactivates (e.g., do not mix with vitamin C). Precipitates in NaCl and G & W with heparin.[200] May increase theophylline serum concentrations.[244] May interfere with digoxin inactivation by gut flora.[102]
Toxicity	Gastrointestinal upset; drug fever; stomatitis; painful injection; IV administration may cause abdominal cramps, nausea, vomiting, dizziness, and sweating.[394] Estolate associated with reversible intrahepatic cholestasis; rare in children.[238] Hepatotoxicity also reported with ethylsuccinate.[386] Deafness has been reported in patients with renal insufficiency.[330] Pseudomembranous

	colitis;[147] hemolytic anemia;[529] interstitial nephritis.[415]
Comment	Oral estolate (lauryl sulfate) is best absorbed. A dose of 10 mg/kg orally gives a peak serum level of 2–6 μg/ml at 2 h.[299] False-positive SGOT elevations by colorimetric method.[426] May be useful with alkali in urinary tract infections due to gram-negative bacteria.[538]

Ethambutol

Spectrum	*Mycobacterium tuberculosis,*[184,203] *M. marinum,* some *M. kansasii* are sensitive.
Dose	15 mg/kg/day: retreatment 25 mg/kg/day for 60 days; then 15 mg/kg/day.
Toxicity	Toxicity rare with 15 mg/kg/day dose. 3% incidence of retrobulbar neuritis with high dose.[106] Patients should be routinely followed with monthly examination of visual acuity and color discrimination. The optic neuropathy is usually reversible.[166] Anaphylactoid reactions; peripheral neuritis; renal damage is rare; increased serum uric acid;[392] thrombocytopenia.[397]
Comment	Experience in children is limited. Adds very little antituberculosis activity to rifampin or isoniazid.

Gentamicin

Spectrum	Most gram-negative rods including *Pseudomonas aeruginosa,* Proteus species, and *Serratia marcescens* are sensitive. Some gram-positive bacteria, including coagulase-negative and -positive staphylococci, but relatively inactive against pneumococci and streptococci. May be useful with penicillin for enterococcus.[510] Inactive against most anaerobic bacteria.
Dose	Oral: 5–10 mg/kg/day (about 0.2% absorbed). Note: Monitor serum levels (keep < 10 μg/ml at peak and < 2 μg/ml at trough). Oral and topical use favors development of bacterial resistance.[163] IM, IV: Newborn[354]—5 mg/kg stat, then 5 mg/kg/day divided q 12 h < 7 days of age, then 6–7.5 mg/kg/day divided q 8 h.[288,295] Use 2.5 mg/kg q 18 h in neonates < 34 weeks.[476] > 2 years: 5 mg/kg/day divided q 6–8 h (may be used in higher dosage up to 7.5 mg/kg/day for brief periods). Intraventricular: 4–8 mg/dose.

	Intrathecal: 1–3 mg/dose. Renal failure: see VI. Miscellaneous.
Incompatibility	Cloudiness with heparin.[200] Should be used with caution in patients receiving other ototoxic or nephrotoxic drugs, i.e., ethacrynic acid.[4] Furosemide probably does not increase the risk of auditory toxicity.[449] Should not be mixed in the same solution with penicillins[411,525] or amphotericin. Combination of chloramphenicol and gentamicin may be antagonistic.[470] Stable in amino acid solutions.[83]
Toxicity	Irreversible vestibular and cochlear damage, most frequent in uremic patients, related to excessive blood levels and prolonged treatment courses. Nephrotoxicity uncommon, related to peak serum levels above 10 μg/ml[242] and to trough levels > 2 μg/ml.[190] Transient proteinuria, elevated BUN, oliguria, azotemia. Fanconi syndrome (proximal tubular injury);[422] Neuromuscular blockade;[389] rash; elevated SGOT. In uremic patients, dose should be modified (see VI. Miscellaneous) and serum levels monitored. Granulocytopenia.[74] Antibacterial activity may be enhanced by mitomycin C but antagonized by bleomycin.[333] May potentiate effects of botulinum toxin.[433]
Comment	Topical gentamicin for superficial infections of the skin, mucous membranes, burns, and eye infections are effective but associated with development of resistance. Bile concentration 37% of serum level.[388] Peritoneal concentration 68% of simultaneous serum level.[408] Due to marked interpatient variations, effects of age, obesity, variable susceptibilities, and poor tissue penetration, quantitative sensitivity testing and pharmacologic monitoring are recommended.[442] More active at alkaline pH.[470] May potentiate neuromuscular weakness in infant botulism.[241] Serum level reduced by approximately 60% by exchange transfusion.[228] Increased dosage requirements in patients with cystic fibrosis.[217]

Isoniazid

Spectrum	*Mycobacterium tuberculosis, M. kansasii* are sensitive.
Dose	Oral: *Therapy*: 10 mg/kg/day (one dose); no greater than 600 mg/day. Usual oral dose for

	pulmonary infection in adults is 300 mg/day. Oral absorbed as well as IM.[371] *Prophylaxis*: 10 mg/kg/day up to 300 mg/day (once daily). IM: 10 mg/kg/day divided q 12 h.
Incompatibility	May increase phenytoin[412] and carbamazepine[46] serum concentrations. Psychosis or ataxia may occur with disulfiram.[412] Antacids (particularly aluminum hydroxide) may decrease absorption; give isoniazid > 1 h before antacid.[196] Alcohol may increase hepatotoxicity[309] and cause nausea, vomiting, headache, and convulsions.[143] Chronic alcohol ingestion may decrease isoniazid effect. Rifampin may increase hepatotoxicity. Patients taking isoniazid have had reactions including severe headache, redness, and itching of eyes and face after eating tuna (due to histamine broken down by bacteria from histidine in tuna and inhibition of diamine oxidase by isoniazid.[357]
Toxicity	Neurotoxic, due to pyridoxine deficiency (rare in children). Gastrointestinal symptoms; seizures;[418] liver damage[65,148,247,344] (rare in children[420] but may be potentiated in young infants by rifampin).[54] Glossitis; Rashes—may be acneiform;[82] positive Coombs test is rare. Hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Depression, agitation, auditory and visual hallucinations, paranoia.[65]
Comment	Adjustment may be necessary in renal failure; monitoring of serum levels is recommended.[50] Rate of hepatic acetylation (rapid in Blacks and Orientals) usually not clinically relevant. Induces antinuclear antibody formation.[416] Overdosage may cause seizures, metabolic acidosis, and coma; pyridoxine reverses effects.[508] Discontinue with symptoms and/or signs of hepatitis or when serum transaminase activity is accompanied by hyperbilirubinemia or elevated alkaline phosphatase *or* reaches three times normal.[326]

Kanamycin

Spectrum	Most *E. coli,* Klebsiella, Enterobacter, Proteus, but very few Pseudomonas species are sensitive. Not active against gram-positive cocci other than some staphylococci. May be synergistic with penicillins for enterococcus and Listeria. Inactive against anaerobes.

Dose

Oral: Approximately 1% absorbed. 50–100 mg/kg/day divided q 6 h.
IM, IV: Newborns:

Birth weight	Age < 7 days	Age > 7 days
≤ 2000 g	7.5 mg/kg/12 h	10 mg/kg/12 h
> 2000 g	10 mg/kg/12 h	10 mg/kg/8 h

Children > 1 month: 30 mg/kg/day divided q 8 h.[180] Aerosol: 1 ml q.i.d. (250 mg/ml). Can cause blood levels as high as 1.5 μg/ml but usually not absorbed.[18] Intrathecal:[300] 5 mg/dose (up to 20 mg/dose has been used).

Incompatibility

Precipitates with heparin in G & W and NaCl.[200] Do not mix with carbenicillin, ticarcillin,[525] or methicillin[412] in the same solution. Unstable in hyperalimentation solutions.[129]

Toxicity

Limit use to 10 days if possible. Irreversible deafness after prolonged high dosage. Cumulative ototoxicity with other ototoxic drugs including ethacrynic acid. Nephrotoxicity transient unless previous renal impairment present. Safe total dosage < 0.5 g/kg. Toxicity at concentrations > 30 μg/ml. May potentiate effects of botulinum toxin.[433]

Comment

Modify dosage and use with caution in oliguric patients (see VI. Miscellaneous), myaesthenia gravis, anesthetized patients, and infant botulism (neuromuscular blockade).[389] Cross-resistance with neomycin.

Lincomycin

Spectrum

Gram-positive organisms except *Streptococcus faecalis* are sensitive. Resistant pneumococci and group A streptococci have been reported. Poor for *H. influenzae* and mycoplasma.

Dose

Oral: 50–100 mg/kg/day divided q 8 h. 22–33 mg/kg gives mean peak serum concentrations of 4–9 μg/ml.
IM: 10–20 mg/kg/day divided q 12 h.
IV: 10–20 mg/kg/day divided q 8 h.
Newborns: do not use in newborns under 1 month of age.

Incompatibility

Do not mix with kanamycin or erythromycin. Kaolin-pectin prevents absorption.[365]

Toxicity	Diarrhea (colitis is rare),[497] nausea, vomiting; rash; urticaria; rectal irritation, vaginitis; SGOT rise;[426] jaundice; neutropenia and/or leukopenia.
Comment	Penicillins, clindamycin, erythromycin, or a cephalosporin are preferred for most infections formerly treated by lincomycin. The evidence for this drug being as good or better than penicillinase-resistant penicillins in osteomyelitis is scanty.[120,183]

Methenamine Mandelate

Indication	Chronic urinary tract infections but effect may be minimal.[492]
Dose	Oral: 50 mg/kg/day divided q 8 h.
Toxicity	Gastrointestinal disturbance. Dysuria, crystalluria.
Comment	Urine should be acid ($<$ pH 5.5) for maximum bacteriostatic effect. Co-trimoxazole (trimethoprim/sulfamethoxazole) or nitrofurantoin preferred.

Methicillin (see also Penicillins)

Spectrum	Penicillinase-producing staphylococci. Less effective than penicillin G for other gram-positive cocci, including non-penicillinase-producing staphylococci.
Dose	IV, IM: 100–200 mg/kg/day divided q 4–6 h. Newborn: 50–100 mg/kg/day divided q 12 h for first 2 weeks in $\leq$ 2000 g and q 8 h in $>$ 2000 g. Then 100–200 mg/kg/day divided q 6 h.
Incompatibility	Tetracycline, kanamycin,[412] neomycin. Deterioration in dextrose/water or normal saline is rapid and is reduced by adding 3 mEq/liter $NaHCO_3$.[531]
Toxicity	Hypersensitivity; renal damage;[204,432] hematuria (thought to be a hypersensitivity phenomenon but may be dose-related in children);[131] reversible bone marrow depression; painful IM; eosinophilia; SGOT elevations.
Comment	If therapy is initiated with methicillin (or other penicillinase-resistant penicillin) because of suspected penicillin resistance, penicillin G should be substituted when sensitivity to this agent is shown. 1 g contains 2.5 mEq Na^+. CSF concentrations poor.[17] Pseudoproteinuria with trichloroacetic acid method.[9]

Metronidazole (see also Antiparasitics—*Entamoeba histolytica*).

Spectrum	Anaerobes are sensitive (some resistance has been noted).[459] Anaerobic streptococci and nonsporulating gram-positive anaerobic bacilli, Propionibacterium, Bifidobacterium, Actinomyces, and Arachnia are often resistant.[370] Parasites and protozoa are sensitive.
Dose	20–30 mg/kg/day divided q 8 h. PO or IV. Newborn: PO or IV, 15 mg/kg loading dose (provides serum concentrations of 20–30 µg/ml for 48 h in < 32 weeks gestation and 10–20 µg/ml for 24 h in term infants), then 7.5 mg/kg q 12 h for the first week of life.[201]
Incompatibility	Alcohol may interact with metronidazole, resultant nausea, vomiting, headache, and convulsion.[143] May increase the effects of anticoagulants.[309] Metabolism may be increased by phenobarbital and by phenytoin.[302]
Toxicity	Gastrointestinal upset, colitis;[428] urticaria; urethral burning; candidiasis; reversible neutropenia; convulsions, ataxia, peripheral neuropathy;[240] carcinogenic potential;[323] metallic taste.
Comment	May cause brownish discoloration of urine. Therapeutic concentrations achieved in saliva, bone, bile, semen, CSF; excreted in milk and crosses placenta.[370] Adjust dose in hepatic dysfunction, since metabolism occurs primarily in liver.

Mezlocillin

Spectrum	Lactamase-negative, gram-positive and gram-negative bacteria are sensitive. Azlocillin more active against *Pseudomonas aeruginosa.*
Dose	IM/IV: 300 mg/kg/day (maximum 24 g/day), divided q 4 h. Infuse IV over 30 min. Newborns: ≤ 2000 g ≤ 7 days: 75 mg/kg q 12 h (150 mg/kg/day) > 7 days: 75 mg/kg q 8 h (225 mg/kg/day) > 2000 g ≤ 7 days: 75 mg/kg q 12 h (150 mg/kg/day) > 7 days: 75 mg/kg q 6 h (300 mg/kg/day)
Incompatibility	See Penicillins.
Toxicity	See Penicillins. Thrombophlebitis with IV administration.
Comment	*Pseudomonas aeruginosa* may develop resistance

during therapy. Contains 1.9 mEq Na^+/g. Limited experience in the pediatric age group.

Minocycline (see Tetracycline)

Moxalactam

Spectrum	Most aerobic and anaerobic bacteria are sensitive in vitro (MIC $\leq$ 16 μg/ml). Methicillin-resistant *S. aureus*, some *S. epidermidis* strains, some strains of group B Streptococcus, most Listeria, most *S. faecalis*, most *C. difficile*, and some Pseudomonas are resistant.
Dose	IV or IM: 100–200 mg/kg/day divided q 6 h. 50 mg/kg q 8 h gives a mean 5-min peak of 257 μg/ml in serum.[414] Newborn: 100 mg/kg/day divided q 12 h for first week of life, then q 8 h. Renal failure: 50 mg/kg/dose q 48 h in anuria and q 24 h with dialysis.
Incompatibility	Aminoglycosides in the same solution.
Toxicity	Hypoprothrombinemia due to inhibition of vitamin K-producing gut flora. Bleeding time prolonged.[512] Disulfiram-like effect when alcohol ingested after drug.[360] Eosinophilia, thrombocytopenia, thrombocytosis, neutropenia; fever; pain with IM injection; phlebitis (2%); morbilliform rash (3%);[534] anaphylaxis; pseudomembranous colitis; elevated SGOT, SGPT; positive Coombs test. See Cephalosporins.
Comment	A third-generation cephalosporin with marked antibacterial activity against gram-negative bacteria and resistance to β-lactamase hydrolysis. Should not be used alone where Staphylococcus, streptococci, Listeria, or Pseudomonas species may be causative. Approximately 15–30% CSF penetration.[212,435] Eliminated by glomerular filtration; unaffected by probenecid.[99] Each gram contains 3.8 mEq Na^+.

Nafcillin (see also Penicillins).

Spectrum	Staphylococci, streptococci are sensitive.
Dose	Oral: poorly absorbed (**Do not use**)[226] IM, IV: 100–150 mg/kg/day divided q 6 h.[133] Newborn: 75 mg/kg/day divided q 8 h for < 2500 g and and < 1 week. 100 mg/kg/day divided q 8 h for other newborns.[25]

Incompatibility	B-complex vitamins.
Toxicity	Thrombophlebitis with IV use. Extravasation injury reported; hyaluronidase infiltration may help avoid injury;[537] neutropenia;[429] anemia. May increase bleeding time due to platelet dysfunction[7]. SGOT elevations; eosinophilia;[132] hypokalemia;[336] interstitial nephritis[48].
Comment	90% of single IV dose excreted via biliary tract [226] and 10% via the kidney. Peak bile concentrations higher than plasma concentration. Mean peak serum concentrations 48 μg/ml 30 min after 37.5 mg/kg IV. Avoid in first 2 weeks of life because liver is major pathway for excretion. Pseudoproteinuria by sulfasalicylic and trichloroacetic acid methods.[11]

Nalidixic Acid.

Spectrum	Useful in some gram-negative urinary tract infections[501] due to *E. coli,* Enterobacter, Serratia, Klebsiella, Proteus species; Pseudomonas is generally resistant.
Dose	Oral: 12 mg/kg/day divided q 6 h. May be poorly absorbed in some patients with diarrhea.[358]
Incompatibility	Increases effect of oral anticoagulants by displacement from binding protein.[309]
Toxicity	Gastrointestinal upset; hypersensitivity (pruritus, rash, urticaria); eosinophilia; seizures, confusion, depression, excitement, visual hallucinations; intracranial hypertension[8]. photosensitivity;[52] hemolysis in glucose-6-phosphate dehydrogenase deficiency.
Comment	Resistance frequently develops. Use cautiously in patients with liver disease and/or impaired renal function. Do not use in children under 1 month of age or for infections other than those of urinary tract. Sensitivities as reported from the bacteriology laboratory correspond to urine, not serum levels. Most active at alkaline pH.[412]

Neomycin

Spectrum	Bactericidal for some gram-positive cocci and gram-negative bacilli.
Dose	Oral: Approximately 3% absorbed:[53] 100 mg/kg/day divided q 6 h. Newborn: Oral 50 mg/kg/day divided q 6 h. Aerosol: 2 ml q 6 h (50 mg/ml). 15 mg/kg/day aerosol may produce toxic blood levels.

Toxicity	Not recommended parenterally because of renal and auditory toxicity. Oral use causes diarrhea, reversible disaccharidase deficiency,[66] malabsorption,[270] candidiasis, colitis, and rarely, deafness.[208] Topical use causes rashes and skin sensitization in 7% of patients.[17,379] Intrapleural or intraperitoneal use can lead to respiratory arrest (curare-like effect) which is potentiated by anesthesia and reversible by neostigmine or Ca^{2+}.[389] Use with caution by all routes in patients with renal and hepatic disease including the relatively oliguric newborn, patients receiving ethacrynic acid or furosemide,[310] in myaesthenia gravis, and in anesthetized patients.

Netilmicin.

Spectrum	Similar to that of gentamicin and tobramycin, but some strains resistant to these aminoglycosides may be sensitive to netilmicin.[164]
Dose	IV or IM, newborn: 2.5 mg/kg q 12 h for infants < 2500 g[38] 3.5 mg/kg q 12 h for infants > 2500 g Children: 3.0 mg/kg q 8 h. Patients with cystic fibrosis have $t_{1/2}$ of 1.4 compared with 2.3 in controls.[332]
Incompatibility	See Gentamicin.
Toxicity	Similar to that of gentamicin, but may be somewhat less ototoxic and nephrotoxic.
Comment	Newly marketed aminoglycoside which is the 1-ethyl derivative of sisomicin. Advantages include antibacterial activity against selected isolates and the potential for less ototoxicity and nephrotoxicity in patients requiring prolonged high doses.[255]

Nitrofurantoin

Spectrum	Many gram-negative bacteria are susceptible to concentrations achieved in urine. Most active at alkaline pH.[412]
Dose	Oral: 5–7 mg/kg/day divided q 6 h. 2.5 mg/kg at bedtime useful for long-term administration in chronic UTI.[267] Macrocrystalline form is associated with fewer adverse reactions.[209]
Incompatibility	Antacids may decrease gastrointestinal absorption.[412] Nausea, vomiting, headache, and, rarely, convulsions when taken with alcohol.[143]

Toxicity	Hemolytic anemia especially in glucose-6-phosphate dehydrogenase deficiency. Peripheral neuropathy (usually seen in diabetes mellitus, renal failure, etc.);[135] rash; chills, fever, myalgia; eosinophilia; pulmonary infiltration;[168] cholestatic jaundice; gastrointestinal disturbances very common.
Comment	Should be used only for urinary tract infections. Sensitivities as reported from the bacteriology laboratory correspond to urine (100 mg P.O. gives urine level of approx. 150 μg/ml), not serum levels. Not recommended IV or for patients with renal impairment[135]. May cause brownish discoloration of urine.

Oxacillin (See Penicillins).

Spectrum	Gram-positive bacteria are sensitive.
Dose	100–200 mg/kg/day divided q 6 h.
Toxicity	Hepatitis[56]. *C. difficile* colitis[55]. Interstitial nephritis[486].

Para-Amino Salicylic Acid (PAS).

Spectrum	*Mycobacterium tuberculosis* is sensitive.
Dose	Oral: 250–300 mg/kg/day divided q 6 h.
Incompatibility	Acetylsalicylic acid (plus PAS) may lead to salicylism.[412] May increase activity of bishydroxycoumarin and dilantin.[412] Probenecid inhibits renal excretion and may increase toxicity. Rifampin serum levels may be lowered by PAS.[398]
Toxicity	Gastrointestinal symptoms; nausea; anorexia; vomiting; diarrhea; malabsorption;[170,270] hypersensitivity (skin rash, fever); leukopenia, thrombocytopenia;[115] hemolysis, especially in patients with glucose-6-phosphate dehydrogenase deficiency. Rarely, suppression of thyroid function. May decrease absorption of fat, folate, and vitamin B_{12}.
Comment	Avoid or reduce dosage when renal function impaired. Urine containing PAS reduces Benedict's reagent. May retard metabolism of dilantin.

Penicillins[17]

Comment	This group of antibiotics inhibits cell wall synthesis, and its members share many molecular and biological properties. Degree of protein binding varies considerably; the significance of

	this property is unclear. Tetracyclines and chloramphenicol may be antagonistic to the penicillins in pneumococcal infections. Probenecid and acetylsalicylic acid increase half-lives. Antibacterial activity may be enhanced by mitomycin C but antagonized by bleomycin.[333] May prolong partial thromboplastin time.[202]
Allergy	All penicillins are cross-allergenic,[162] but this bears little relationship to atopy in general.[440] Penicilloyl-polylysine and aqueous penicillin G [scratch tests with 5 then 10,000 units/ml, followed by intradermal test (I.D.) with 10,000 units/ml] will identify most patients likely to have an immediate hypersensitivity reaction.[324] Use saline controls and a 20-min interval between tests. To desensitize when penicillin must be used in the presence of penicillin sensitivity:[312] 1. I.D.: 0.1 ml of solution of 1000 units/ml. 2. Double concentration q 20 min until 50,000 units. 3. Repeat subcutaneously from 1000 to 50,000 units. 4. If no reaction, proceed with continuous IV therapy, under close supervision. An alternate (?safer) program can be used in patients able to take drugs orally, although 4 h are required.[356] Give 13 doses of penicillin G oral suspension starting with 100 units and double the amount every 15 min until 400,000 units. Then give subcutaneous shots of 2, 4, and 8 hundred thousand units every 15 min. Finally give 1 million units IM.
Toxicity	In general, toxicities are not dose-related. Hypokalemia, hyperkalemia, CNS irritation with myoclonic convulsions, and superinfection are exceptions. Rashes (maculopapular, erythematous and often pruritic) occur in 5–10% but have no pathognomonic features. Urticaria is less common. Leukopenia may occasionally be observed,[351] as may antabuse-like reactions.[107]

Penicillins rendered ineffective by penicillinases: amoxicillin, ampicillin, azlocillin, bacampicillin, carbenicillin, cyclacillin, mezlocillin, penicillin G, phenoxymethyl penicillin, piperacillin, procaine penicillin, ticarcillin. *Penicillins resistant to penicillinase:* cloxacillin, dicloxacillin, methicillin, nafcillin, oxacillin.

Benzathine Penicillin

Dose	Oral: poorly absorbed. IM: 600,000–1,200,000 (every 4 weeks for rheumatic fever prophylaxis). Newborn: 50,000 units/kg may be adequate for some streptococcal infections[227] and primary syphilis. Do not use for neurosyphilis.[455]
Comment	Useful in rheumatic fever prophylaxis. Raising dose gives a more sustained rather than a higher blood level.

Benzyl Penicillin (G): Potassium or Sodium Salt

Spectrum	Gram-positive and gram-negative cocci, gram-positive bacilli are sensitive. In high doses, some gram-negative organisms such as *E. coli* and *Proteus mirabilis* in the urinary tract[195] are sensitive.
Dose	Oral: 100,000–400,000 units/dose in 4 doses, ½ h before or 2 h after meals. Antacids may decrease absorption.[412] 1 unit = 0.6 μg, 1600 units = 1 mg. An oral dose of 8 mg (approximately 12,500 units)/kg gives a peak serum concentration of 0.5–1.5 μg/ml at ½ h, fasting.[299] IM or IV: 20,000–500,000 units/kg/day divided q 4–6 h. CSF concentrations are low, e.g., the mean peak CSF concentration is 0.96 μg/ml after 250,000 units/kg/day in children with meningitis.[181] Newborn: 50,000–150,000 units/kg/day divided 12 h in first weeks, then q 8 h[298]. Intrathecal, intraventricular, rare indications, 1–5 ml/24 h (1000 units/ml).
Incompatibility	Do not mix with amphotericin B, metaraminol, phenylephrine, tetracycline, vancomycin, vitamin C, bisulfite.[412] Acid pH inactivates.
Toxicity	Hypersensitivity (anaphylaxis, urticaria, rash, drug fever);[5,78,161] change in bowel flora; diarrhea; moniliasis; hemolytic anemia.[410] Neurotoxic in very large doses, especially with renal failure.[399]
Comment	One million units of potassium penicillin G contains 1.7 mEq K+. Avoid pushing large doses of K+ salt, as in initiating therapy for meningitis; use Na+ salt instead (contains 1.7 mEq Na+/1 million units). Half-life increased significantly by probenecid and phenylbutazone and to a lesser degree by sulfonamides and acetylsalicylic acid.[210] False-positive proteinuria.[9]

Phenoxymethyl Penicillin (Penicillin V)

Dose Oral: 50,000–400,000 units/kg/day (32–250 mg/kg/day) divided q 6 h (except for newborn—q 12 h). A dose of 8 mg/kg (approximately 12,500 units/kg) gives a peak serum concentration of 1–3 µg/ml at ½ h, fasting.[299]

Comment Better acid stability, more reliable absorption than benzyl penicillin.

Procaine Penicillin

Dose 100,000–600,000 units q 12–24 h.

R_x congenital syphilis: 50,000 units/kg/day × 10 days. This dose gives peak (4 h) serum concentrations of 20 µg/ml and peak (12 h) CSF concentrations of 0.7 ± 0.35 µg/ml.[454] Newborn: do not use (causes sterile abscesses). Also contains 120 mg procaine/300,000 units penicillin G.

Toxicity Hallucinations, disorientation, agitation, bizarre behavior.[112]

Piperacillin

Spectrum A semisynthetic penicillin active against gram-positive and gram-negative bacteria including Pseudomonas species, enterococcus, and most anaerobes. Inactivated by gram-positive and gram-negative β-lactamases. In vitro susceptibility testing recommended.

Dose IM or IV

Age (days)	Weight (g)	Dosage[484]
up to 7	under 2500	50 mg/kg q 8 h
7–14	under 2500	50 mg/kg q 6 h
15–30	2500 and over	75–100 mg/kg q 6 h
> 1 months		50–75 mg/kg q 4 h

Mean peak serum concentration after 50 mg/kg IV = 166 µg/ml.[484]

Incompatibility Inactivation of aminoglycosides in same solution or in patients with severe renal failure.

Toxicity Cross-allergic with penicillins. Diarrhea; bleeding due to reduced vitamin K and decreased platelet aggregation;[149] superinfections; hypokalemia; thrombophlebitis at injection site; vomiting; cho-

	lestatic hepatitis; bloody diarrhea;[322] prolonged muscle relaxation;[322] eosinophilia; neutropenia; thrombocytopenia.
Comment	Contains 1.9 mEq Na^+/g. There is some risk of development of resistant gram-negative bacteria in vivo.[524] Good biliary concentrations (> 3000 μg/ml after 4 g dose). Excreted by glomerular filtration, renal tubular secretion, and in bile. *t*1/2 30–60 min. Protein binding 16%.

Polymyxin B

Spectrum	Pseudomonas species; other gram-negative bacteria as determined by sensitivity testing.
Dose	Oral: **Not absorbed.** 15–20 mg/kg/day divided q 6 h. IM, IV: 3.5–5 mg/kg/day divided q 8 h. Do not exceed 200 mg/day. Newborn: IM, IV—3.5–4 mg/kg/day divided q 6 h. Intrathecal, intraventricular: ≤ 2 years: 2 mg/day or every other day (0.5–1.0 mg/ml). > 2 years: 5 mg/day or every other day. Intraarticular, intraperitoneal, rare indications—1.0 mg/ml.
Incompatibility	Cephalothin, chloramphenicol, heparin, tetracycline. Nephrotoxicity may be increased with aminoglycosides.[412]
Toxicity	Pain at injection site. Aerosol may induce bronchospasm.[101] Neurotoxicity (paresthesias, ataxia, drowsiness); nephrotoxicity (cylinduria, hematuria, proteinuria, raised BUN); fever; rash[245]. Neuromuscular blockade may be reversed with Ca^{2+}. Caution in myaesthenia gravis, renal disease, or anesthetized (succinylcholine) patients (neuromuscular blockade).[85,389] Up to 10% may be absorbed from gastrointestinal tract.
Comment	When treatment of systemic infections due to apparently susceptible strains is being considered, compare the results of disk diffusion test with tube dilution.[291] Due to toxicity and poor tissue penetration, consider alternate drugs before using polymyxin or colistin systemically.

Pyrazinamide

Spectrum	*Mycobacterium tuberculosis* is sensitive.
Dose	Oral: 15–30 mg/kg/day (2 g maximum).
Toxicity	Nausea and vomiting; hepatotoxic; hyperuricemia; arthralgia.

Comment	Useful in patients infected with resistant tuberculosis strains.

Rifampin[398]

Spectrum	Active against gram-positive,[265] gram-negative bacteria. *Mycobacterium tuberculosis*[400,437] and atypical mycobacteria are sensitive.[424] Very effective in the treatment of human tuberculosis,[364] particularly in combination with isoniazid.[398]
Dose	Oral: 15 mg/kg/day (up to 600 mg) in one dose. Better absorbed in fasting state.[443] Reduce dose in patients with liver disease.[3] *For prophylaxis of meningococcal contacts:* Adults: 600 mg twice daily for 2 days. Children: 1–12 years 10 mg/kg twice daily for 2 days. Infants: < 1 year, 5 mg/kg twice daily for 2 days. *For prophylaxis of H. influenzae type b contacts:* 20 mg/kg/day (single dose) × 4 days (max. 600 mg).
Incompatibility	Probenecid blocks hepatic uptake and increases serum concentrations.[221] May decrease effectiveness of oral contraceptives, barbiturates, and anticoagulants (increased liver metabolism).[372] PAS may lower serum levels of rifampin.[398] Increase catabolism of corticosteroids[292] and digitoxin.[391] Phenobarbital may decrease serum levels. May antagonize vancomycin against *S. aureus*.[509]
Toxicity	Headache; drowsiness; gastrointestinal disturbances; pseudomembranous colitis;[328] rise in SGOT; cholestatic jaundice; may potentiate isoniazid hepatotoxicity in young infants;[54] eosinophilia; thrombocytopenia; fever; rashes; elevated prothrombin time;[437] hemolysis;[246] contraindicated in first trimester of pregnancy. Interstitial nephritis with reversible acute renal failure has been reported.[402] Light-chain proteinuria.[157] Acute renal failure with intermittent dosage.[142]
Comment	Rapid development of resistance limits its use in bacterial infections other than mycobacteria and in prophylaxis of meningococcal carriers. May be immunosuppressive (cell-mediated immunity and macrophage function).[329,522] Decrease in serum concentration with prolonged administra-

tion.[36] Excreted into the bile and urine. Diffuses well into CSF (about 20% of serum concentration in acute meningitis).[95,445]

Note: Urine, feces, saliva, sweat, tears and contact lenses may be stained red-orange.[453]

Spectinomycin[407,438,452]

Spectrum	*N. gonorrhoeae* and some gram-negative bacteria in urinary tract infections are sensitive.[507] Rapid resistance developing with use may be a problem.
Dose	For the treatment of gonococcal urethritis in patients allergic to penicillin or infected with penicillin-resistant strains, 40 mg/kg in a single IM dose (maximum 4 g).
Toxicity	Rash;[438] stomatitis; dizziness; burning at injection site.
Comment	An aminoglycoside with potential toxicities that should be reserved for the treatment of gonorrhea. Ineffective for syphilis.

Streptomycin

Spectrum	*M. tuberculosis, M. marinum, M. kansasii, H. influenzae,* some gram-negative bacteria, Brucella. Synergistic with penicillin against enterococci and Listeria. Resistance develops quickly.
Dose	IM: 20–40 mg/kg/day divided q 12–24 h. Newborn: 10–20 mg/kg/day. Single dose.
Toxicity	Damage to vestibular apparatus; ototoxicity; CNS and respiratory depression; neuromuscular block;[389] reversed by neostigmine; bone marrow depression; renal toxicity; hypersensitivity. Caution in myaesthenia gravis, renal disease, and anesthetized patients (neuromuscular blockade). Toxicity may be associated with serum concentrations above 40 μg/ml.
Comment	Usually should not be used as the only drug. May give false-positive reaction for glucose in urine using copper sulfate solution (Benedict's reagent, Clinitest®).

Sulfonamides[526]

	Sulfadiazine, sulfisoxazole, sulfamethoxazole, triple sulfa, sulfathiazole (see also Trimethoprim-sulfamethoxazole).
Spectrum	Bacteriostatic against selected gram-positive and

	gram-negative organisms and Nocardia. Most active and soluble at an alkaline pH.
Dose	*For sulfadiazine, triple sulfa, sulfisoxazole*[493,494] Oral: 120–150 mg/kg/day divided q 6 h. Absorption decreased by antacids.[412] 20–30 mg/kg/day for prophylaxis of urinary tract infection.[111] IV: 120 mg/kg/day divided q 6–12 h (alkaline urine to prevent crystalluria). Newborn: **Do not use.** *For sulfamethoxazole* Oral: 25–50 mg/kg/day divided q 12 h.
Incompatibility	May displace bilirubin and the following drugs from binding protein: tolbutamine → hypoglycemia, warfarin or bishydroxy-coumarin → bleeding, methotrexate → toxicity.[412]
Toxicity	Crystalluria: **Keep fluid intake high.** Hypersensitivity (fever, rash, hepatitis, lupus-like state, vasulitis);[254] neutropenia, aplastic anemia, thrombocytopenia;[177] hemolytic anemia in glucose-6-phosphate dehydrogenase deficiency. Kernicterus in newborns. Rare interstitial nephritis. Photosensitivity. Stevens-Johnson syndrome and lupus-like reactions have been reported even with topical (e.g., ophthalmic sulfacetamide) application.[308]
Comment	Useful in infections of urinary tract, and for rheumatic fever prophylaxis (do not give to pregnant women during third trimester). Should not be relied upon for treatment of group A streptococcal infections. Long-acting preparations more frequently associated with serious hypersensitivity reactions. Sulfadiazine is preferred for CNS infections as diffusion into CSF is better.

Tetracyclines[347]

Spectrum	Gram-positive (tetracycline-resistant group A streptococci and pneumococci have been reported with increasing frequency) and some gram-negative bacteria, rickettsia, chlamydia and mycoplasma. Cross-resistance is seen with all tetracyclines. Minocycline may be more effective against Staphylococcus and Nocardia than other tetracyclines.[21]
Dose[26]	*Tetracycline, chlortetracycline, oxytetracycline* Powder-filled capsules better absorbed than tablets.[96]

	Oral: 20–40 mg/kg/day divided q 6 h. IM, IV: 12 mg/kg/day divided q 12 h (IM achieves poor levels; painful). *Demethylchlortetracycline* Oral: 12 mg/kg/day divided q 6 h. *Minocycline, doxycycline* Oral: 4–5 mg/kg/day divided q 12 h.
Incompatibility	Milk or antacids.[361] Amphotericin B, alkaline solutions.[412] Ca^{2+}, cephalothin, chloramphenicol, heparin, hydrocortisone, methicillin, penicillin G, polymyxin B, vitamin B_{12}.[309,412] Iron, Zn^{2+}, Ca^{2+}, Mg^{2+}: all may decrease oral absorption,[361,412], as may cimetidine.[84] Methoxyflurane (penthrane) may increase nephrotoxicity.[309,412] Barbiturates, carbamazepine, and hydantoins may reduce half-life of doxycycline by liver enzyme induction.[362,383] May decrease efficiency of oral contraceptives.[489] Subsalicylate bismuth may reduce the absorption of doxycycline.[119]
Toxicity	In children under 8 years, may cause damage to teeth (reflected by discoloration) and bone.[165] The risk is greatest in those under 4 years and in those receiving high doses and multiple courses. Deposition in teeth and bone of premature and newborn infants can result in enamel dysplasia and growth retardation. Outdated tetracycline can produce Fanconi syndrome. Benign intracranial hypertension; nausea, vomiting, diarrhea, stomatitis, glossitis, proctitis; candidiasis; overgrowth of staphylococci in bowel; disturbed renal function and nephrogenic diabetes insipidus with demethylchlortetracycline;[269] drug fever, rash, photosensitivity,[45] blue-gray skin discoloration with minocycline;[136] hepatotoxicity.[264] May decrease leukotaxis, neutrophil mobility,[277] and phagocytosis.[156] Vestibular symptoms common with minocycline;[340] photoonycholysis;[249] myopathy.[444]
Comment	Useful in treatment of rickettsial infections, psittacosis, brucellosis, Bacteroides (less active than chloramphenicol or clindamycin), mycoplasma infections. Doxycycline most useful in renal failure (for indications other than urinary tract infection) as half-life unaffected.[214] May interfere with bactericidal effect of serum.[145] Doxycycline penetrates sinuses well.[117]

Ticarcillin

Spectrum	Similar to carbenicillin but twice as active against *Pseudomonas aeruginosa.* Cross-resistance with carbenicillin. Frequently synergistic with aminoglycosides against Pseudomonas.
Dose[352]	Newborns: ≤ 2000 g: 150 mg/kg/day divided q 12 h for first week. > 2000 g: 150–225 mg/kg/day divided q 8 h to age 2 weeks, then 300 mg/kg/day (maximum 18 g) divided q 4–6 h. 300 mg/kg/day gives a peak serum concentration of 180 μg/ml; sputum, 5 μg/ml.[377]
Incompatibility	Inactivates aminoglycosides when mixed in same bottle. Such combinations may also result in lower serum levels of aminoglycosides and ticarcillin in patients with renal failure.[77]
Toxicity	Similar to that of carbenicillin. Inhibition of platelet function with high doses; hypokalemia; teratogenic in mice. 5.2 mEq Na^+/g. Hepatotoxicity;[158] granulocytopenia.[369]

Tobramycin[86]

Spectrum	Similar to that of gentamicin but more active against *Pseudomonas aeruginosa.*[250] Active against some gentamicin-resistant bacteria.
Dose	Newborns: 5 mg/kg IV or IM stat,[288] then 5–7.5 mg/kg/day divided q 12–24 h, < 1 week, and q 8–12 h thereafter.[12] > 1 month 8–10 mg/kg/day divided q 8 h.[186]
Incompatibility	See Gentamicin. Less inactivated by piperacillin than by carbenicillin or ticarcillin, even in normal subjects.[233]
Toxicity	Same as that of other aminoglycosides; see Gentamicin. Concentrations above 10 μg/ml may be toxic. Less nephrotoxic in adults than gentamicin.[450] May potentiate effects of botulinum toxin.[433] Delerium.[293]
Comment	Significantly cleared by peritoneal dialysis. Monitoring of serum levels recommended.[278] May be excreted more quickly in patients with major burns.[268] Increased dosage requirements in patients with cystic fibrosis.[219]

Trimethoprim

Spectrum	*E. coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter sp.* are sensitive.
Dose	Oral: 100 mg b.i.d. for acute urinary tract infections in patients over 12 years of age.
Incompatibility	See Trimethoprim-Sulfamethoxazole.
Toxicity	See Trimethoprim-Sulfamethoxazole.
Comment	Limited experience in the treatment of urinary tract infections in adults.[263] Development of resistant bacteria is a potential risk of frequent use.[64]

Trimethoprim (TMP)—Sulfamethoxazole (SMZ)[405]

Spectrum	This combination acts by sequential blockage of bacterial folate metabolism.[405] Effective against gram-negative bacteria including some *E. coli,* Proteus, Klebsiella, Enterobacter, Salmonella,[287] Shigella.[419] Ineffective against *Pseudomonas aeruginosa.* Some strains of *Nocardia asteroides* and *Serratia marcescens* have been reported to be sensitive. Effective against *Pneumocystis carinii.*[192]
Dose	Oral or IV (over 60–90 min): *therapy*: 5–10 mg TMP/25–50 mg SMZ/kg/day divided q 8–12 h. TMP 4 mg/kg and SMZ 20 mg/kg PO gives mean peak in serum of 2/45 and in serous middle ear fluid 1.4/8 μg/ml.[229] Newborns and infants under 2 months (rarely indicated): IV TMP 2 mg/10 mg SMZ loading dose followed by TMP 1 mg/SMZ 5 mg q 12 h.[458] *UTI prophylaxis*$_1$: 2 mg TMP/10 mg SMZ/kg/day (one dose at bedtime).[111] Pneumocystis prophylaxis: 4 mg TMP/20 mg SMZ/kg/day, divided twice daily. *Pneumocystis treatment*: 20 mg TMP/100 mg SMZ/kg/day (divided q 8 h) × 14 days, PO or IV. CSF penetration approximately 50% in children with hydrocephalus.[506]
Incompatibility	Hemolysis with glucose-6-phosphate dehydrogenase deficiency. Anemia with pyrimethamine or other antifolate (e.g., methotrexate).[141] May potentiate warfarin and phenytoin due to inhibition of hepatic metabolism.[176] Like other sulfonamides, may potentiate oral hypoglycemics. May lower cyclosporin serum concentrations.[504]

Toxicity	Rash; fixed (recurs at same site) genital drug eruption.[477] Stevens-Johnson syndrome.[319] Nausea, vomiting, diarrhea, pseudomembranous colitis;[381] thrombocytopenia, leukopenia, anemia, pancytopenia[490] (can be seen with trimethoprim alone);[439] nephrotoxicity;[451] hepatotoxicity;[349,464] cholestasis;[151] alkaline phosphatase elevation;[100] pancreatitis; lymphadenopathy; splenomegaly;[79] fever; confusion, depression, hallucinations;[319] thrombophlebitis rare after IV administration.
Comment	Dosage needs to be adjusted with severe impairment of renal function.[91] Useful in treating urinary tract infection but minor side effects up to 20%.[57] May increase hyperphenylalaninemia.[252] May have antithyroid effect (lowering of thyroid hormone concentrations).[81]

Vancomycin[150]

Spectrum	Staphylococci, other gram-positive cocci, clostridia, corynebacteria. Main use is in treatment of staphylococcal and clostridial colitis and methicillin-resistant staphylococcal infection.[88,513]
Dose	Newborn: IV over 30–60 min, 30 mg/kg/day divided q 12 h for 1st week, then q 8 h.[434] Oral: **Not absorbed.** 50 mg/kg/day divided q 6 h. IV: over 60 min, 40 mg/kg/day divided q 8–12 h. 10–15 mg/kg dose gives mean peak serum concentration of 25–30 μg/ml.[434] Intraventricular: 5 mg.[87]
Incompatibility	Do not mix with chloramphenicol, methicillin, heparin, hydrocortisone, and penicillin G. May antagonize rifampin against *S aureus*.[509] May potentiate nephrotoxicity of aminoglycosides.[123]
Toxicity	Painful IM. Troublesome symptoms during IV administration include nausea, chills, thrombophlebitis, fever.[123] Addition of 20 mg hydrocortisone to IV solution may reduce these effects. Peripheral neuropathy (usually serum concentration above 30 μg/ml). Eosinophilia; neutropenia;[223] nephrotoxicity and irreversible ototoxicity have occurred. Ototoxicity has been reported with normal renal function and serum concentrations of > 40 μg/ml at peak and > 30 μg/ml at trough.[488] Hypotension with rapid IV administration.[363] Rash in 1–3%.[123]

Comment	Useful for treatment of methicillin-resistant staphylococci and in penicillin/cephalosporin intolerant patients for serious staphylococcal infections and, with an aminoglycoside, in streptococcal endocarditis. Monitor dose and toxicity.[88] CSF penetration with shunt infection 7–21%.[434] Not removed by peritoneal dialysis.[275]

II. Antifungals[34,331]

Amphotericin B[35]

Spectrum	A variety of fungi (candida, cryptococcus, blastomyces, coccidioides, histoplasma) are sensitive.
Dose	IV: 0.5–1.0 mg/kg/day or every other day, given over 6 h or longer in 5% G & W with a small gauge needle. Build up to this dosage over 3–7 days as clinical condition permits. Start with first dose of 0.5–1 mg. If tolerated, build up dose by doubling amount every other day. If the patient is critically ill, start with 0.2 mg/kg/ on day 1 and 0.5 mg/kg on day 2. Maintain drug concentration less than 100 μg/ml infusion fluid. Intrathecal (used for coccidioidal meningitis): start with 0.05–0.1 mg. Increase to 0.5–1 mg every third day. This dose can also be used for joint space infections.
Incompatibility	Penicillin G or tetracycline. May antagonize antifungal effect of miconazole.[231] Curariform drugs and digitalis may be potentiated by hypokalemia; commonly encountered with amphotericin administration.[309] Antagonistic with miconazole against candida.[316] May cause pulmonary interstitial infiltration and hypoxemia when combined with leukocyte transfusions.[530] Do not mix in the same solution with aminoglycoside or normal saline.
Toxicity	Chills, fever, malaise; significant renal (glomerular and tubular), hepatic, and bone marrow damage.[380] Nephrotoxicity may be reduced by sodium repletion.[128] Thrombophlebitis; calcifications; hypokalemia;[279] hypomagnesemia; hemolytic anemia; leukopenia;[463] thrombocytopenia;[68] cardiac arrhythmia; delerium.[303,523]

	Myelopathy[68] and parkinsonism[138] after intrathecal dosing.
Comment	Administration of aspirin or antihistamines before the daily dose may ameliorate side effects. Add 25 mg hydrocortisone to infusion if the side effects persist. Heparin, added to the infusion, may decrease thrombophlebitis. Meperidine may also be used in low dosage and in older patients. Blood levels should be followed.[42,108] Penetrates bronchial secretions and other body fluids poorly.[382] Combined 5-fluorocytosine-amphotericin therapy may be synergistic and useful in reducing toxicity and delaying emergence of resistance.[491] Amphotericin has been shown to inhibit neutrophil phagocytosis of candida.[71] Teratogenicity has not been documented.[199]

Clotrimazole	Moderately active against a variety of deep and superficial fungi in vitro.[290] Gastrointestinal upset, hepatic and adrenal toxicity, and progressive decline in serum concentrations (liver metabolism) and low urine concentrations limit clinical usefulness systemically.[62,188] Topical therapy (1%) may be useful for superficial dermatophytes and candida infections of the skin.[311]

Flucytosine (5-Fluorocytosine)[35,386,461,495]

Spectrum	Some strains of *Cryptococcus neoformans,* Candida species and *Torulopsis* (*Candida*) *glabrata.*[286] In vitro sensitivity testing is recommended.
Dose	Oral: 150 mg/kg/day divided q 6 h [gives peak serum concentration of approximately 50–100 μg/ml).[231]]
Toxicity	Leukopenia, thrombocytopenia, agranulocytosis (rare). Rises in SGOT and SGPT; gastrointestinal upset. Development of resistance in vivo; hallucinations; serum concentrations above 100 μg/ml should be avoided.[231]
Comment	Half-life in anuria increases from 2 to 4 h to 85 h.[436] Follow hemodialysis with a dose of 20 mg/kg.[231] Penetrates bronchial secretions and CSF well.[382] May be synergistic with amphotericin B against certain yeasts (e.g., candida, cryptococcus). Marrow aplasia reported with combined

therapy in patients with hematologic neoplasms.[58]

Griseofulvin

Spectrum	Dermatophytes are sensitive. Ineffective against deep mycoses.
Dose	Oral: 20 mg/kg/day divided q 6–12 h. (microcrystalline form): 15 mg/kg/day divided q 12 h. Absorption may be enhanced by fat-containing food, such as milk.[154]
Incompatibility	Depresses oral anticoagulant activity (warfarin)[412] probably due to induction of liver metabolizing enzymes.[365] Phenobarbital reduces adsorption[409] and activity.[412] Nausea, vomiting, headache, and possibly convulsions with alcohol.[143]
Toxicity	Leukopenia and other blood dyscrasias. Headache, incoordination, confusion; gastrointestinal disturbances; rash (allergic and photosensitive); renal damage; lupus-like syndrome is rare.
Comment	Do not use in patients with hepatocellular failure or porphyria. Carcinogenicity has been demonstrated in mice.[318]

Haloprogin[305]

Spectrum	Superficial dermatophytes—tinea pedis and corporis.
Comment	Topical drug equivalent to tolnaftate in use and efficacy. May cause skin irritation. Up to 15% has been recovered from urine. Toxic effects of absorbed drug are not yet known.

2-Hydroxystilbamidine[35]

Spectrum	Used to treat North American blastomycosis. Amphotericin B usually preferred.
Dose	150–225 mg IV q.d. given over 6 h (to avoid hypertension). Total dose usually 8–16 g over 2–3 months.
Toxicity	Malaise; anorexia; nausea; paresthesias; hepatic dysfunction; headache; rash.
Comment	Infusion bottle should be shielded from light.

Iodides (Potassium)

Spectrum	*Sporothrix schenckii.*
Dose	Oral: 30–150 drops/day (divided q 8 h) of saturated solution (1 g/ml).

Toxicity	Rash; gastrointestinal disturbances; iodism (bitter taste, excessive lacrimation, swollen salivary glands, acneiform rash) is rare.[35]
Comment	Therapy of localized sporotrichosis responds best. Usual duration is 4–6 weeks after clinical healing[374] Begin treatment with 1–5 drops t.i.d. and increase slowly to maximal dose.[273] Contraindicated in pregnancy. Amphotericin B may be necessary for disseminated infection.

Ketoconazole

Spectrum	*Candida albicans, Coccidioides immitis, Histoplasma capsulatum* are sensitive. Zygomycetes (Rhizopus, Mucor) and Sporotrichum are resistant.[118]
Dose	Oral: 5 mg/kg/day in one dose (maximum 800 mg/day). Absorbed best fasting.[281] Peak (3 μg/ml) occurs 2 h after an oral dose of crushed tablets in applesauce; suspension gives a peak of 5 μg/ml 1 h after a 5 mg/kg dose.[153]
Incompatibility	Decreased absorption with antacids, cimetidine, anticholinergics, and H_2-blockers. May antagonize antifungal effect of amphotericin B.[472] May increase serum concentrations of cyclosporin (and risk of nephrotoxicity), due to inhibition of liver enzymes.[137]
Toxicity	Nausea, vomiting in 3%; abdominal pain, pruritus in 1%; headache, dizziness, somnolence, fever, chills, photophobia and diarrhea in less than 1%; transient elevation in liver enzymes, hepatitis;[179] teratogenic in rats; gynecomastia and adrenal suppression.[390]
Comment	Poor CSF penetration and minimal urine concentrations. Decreased absorption and low peritoneal fluid levels in patients on peritoneal dialysis.[75] Metabolized in liver and excreted in bile; unaffected by renal failure.[51] Useful in chronic mucocutaneous candidiasis, although maintenance therapy required[160] and emergence of resistant Candida has been described.[189] Serum ketoconazole levels may decline during continued treatment in bone marrow transplant recipients.[172]

Miconazole[178]

Spectrum	Water-insoluble imidazole derivative active against *Candida albicans* (0.5–4 μg/ml), *Torulopsis (Candida) glabrata, Coccidioides immitis, Aspergillus,*

	and *Trichosporon sp.*, and superficial dermatophytes.
Dose	Topical: Miconazole nitrate (2%) cream b.i.d. IV: 30 mg/kg/day (divided q 8 h)—infuse over 60 min well diluted in saline or water (peak serum concentrations approximately 7.5 μg/ml).[231] Intrathecal: 20 mg/day (gives CSF concentration of approx. 1 μg/ml).[231] May be antagonistic with amphotericin B.[231]
Incompatibility	Increases effect of oral anticoagulants.
Toxicity	Some local burning; pruritus; rash; fever; chills; nausea; vomiting; phlebitis;[139] thrombocytosis, thrombocytopenia, anemia; hyponatremia; renal insufficiency;[321] tremors, seizures;[205] hypotension, cardiorespiratory arrest; anaphylaxis.[121]
Comment	Poor penetration into urine, sputum, and CSF[146] but good in joints and vitreous fluids. Intravenous administration associated with hyperlipidemia.[22] Absorption poor after oral administration. Some activity against gram-positive and anaerobic bacteria.[178] Poor *in vivo* activity against cryptococcus. Metabolized; no adjustment needed in oliguria or after dialysis.

Nystatin[6]

Spectrum	*Candida albicans* and other yeasts.
Dose	Oral: **Not absorbed.** Newborn: 200,000–400,000 units/day. ≤ 2 years: 400,000–800,000 units/day. > 2 years: 1–2 million units/day divided q 6–8 h. Eye and skin: 100,000 units/g.
Toxicity	Allergic reactions; gastrointestinal disturbances.

Tolnaftate

Spectrum	Superficial dermatophytes (trichophyton, microsporum, and epidermophyton) are sensitive.
Dose	1–2 drops or 1% cream 2–3 times/day.
Toxicity	Mild skin irritation.

III. Antiparasitics[304,345,346]

Note: Mebendazole may be used as a drug of choice for most intestinal nematodes (ascaris, trichuris, hookworm, pinworm) except strongyloides[76]. Also active against echinococcus and many tapeworms (experimental). See *Trichuris trichiura* for details.[47] See reference 304 for parasites not listed below and for a more complete listing of toxicities. For amebic infections due to Naegleria and Acanthamoeba sp., see Amphotericin B; also see *Entamoeba histolytica.*

Ancylostoma duodenale (Hookworm)

Drug	Pyrantel pamoate.
Dose	Oral: 11 mg/kg (maximum 1 g), one dose.
Toxicity	Gastrointestinal upset; headache; dizziness; rash; fever.
Alternate drugs	Mebendazole 100 mg b.i.d. × 3 days (see *Trichuris trichiura*).

Ascaris lumbricoides

Drug	Piperazine citrate.
Dose	Oral: 75 mg/kg in a single dose for 2 days (maximum 3.5 g/day).
Toxicity	Dizziness; urticaria; gastrointestinal upset; exacerbation of epilepsy; visual disturbance; ataxia.
Alternate drugs	Mebendazole 100 mg b.i.d. × 3 days[282] (see *Trichuris trichiura*). Pyrantel pamoate: 11 mg/kg, one dose.

Clonorchis

See Schistosomas.

Diphyllobothrium latum

(See *Taenia saginata*).

Echinococcus granulosus-Echinococcus multilocularis

Drug	Mebendazole 40 mg/kg/day × 1–6 months[224] (see *Trichuris trichiura*).
Comment	Surgery often required.[521]

Entamoeba histolytica[230,304]

Drug	Metronidazole. Add diiodohydroxyquin or emetine in severe infections[230] (see alternate drug for dose) or chloroquine phosphate (see refs. 304 and 230 for details).
Dose	35–50 mg/kg/day divided q 8 h up to 2 g/day maximum × 10 days.
Toxicity	Headache; dry mouth; metallic taste; stomatitis; nausea, vomiting, diarrhea; insomnia; weakness; paresthesias; rash; disulfiram effect with alcohol; leukopenia.[230]

Comment	Metronidazole is carcinogenic in animals and caution is urged in use in human therapy.[323] Urine may be brownish-red.[230] (See also Metronidazole).
Alternate drugs	Diiodohydroxyquin 30–40 mg/kg/day divided q 8 h × 20 days (max. 2 g/day) or diloxanide furoate for asymptomatic cyst excretors[237] (20 mg/kg/day divided t.i.d. × 10 days). In the U.S. the latter available through CDC, Atlanta.

Enterobius[60]

Drug	Pyrantel pamoate: 11 mg/kg (max. 1 g). Repeat after 2 weeks. Menbendazole: 100 mg, single dose, repeat after 2 weeks.

Giardia lamblia

Drug	Quinacrine hydrochloride. Furazolidine highly effective and better tolerated in children under 5 years.[90]
Dose	Quinacrine hydrochloride: 7 mg/kg/day (divided t.i.d.) × 5 days (maximum 300 mg/day).
Toxicity	Quinacrine hydrochloride: dizziness; headache; bitter taste; vomiting. Toxic psychosis; psoriasis-like or exfoliative rash; blood dyscrasias; transient yellow staining of skin and nail pigmentation in young children; urticaria; minor antabuse-like symptoms with alcohol. Furazolidine: Nausea, vomiting, diarrhea; hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency; hypotension; urticaria; brown coloring of urine.[528]
Comment	$NaHCO_3$ may reduce nausea and vomiting. Furazolidine may cause brownish discoloration of urine.
Alternate drugs	Metronidazole (see *Entamoeba histolytica*). Furazolidine 8 mg/kg/day in 3 divided doses × 10 days.[90]

Hymenolepsis nana; See Taenia

Leishmaniasis

Drug	Stibogluconate sodium: 10 mg/kg/day IV or IM (maximum 600 mg/kg/day) × 6–10 days.
Toxicity	Myalgia; arthralgia; bradycardia; diarrhea; colic;

rash; pruritus; myocarditis; hepatitis; hemolytic anemia; renal damage; shock; sudden death.

Necator americanus (Hookworm)

Drug	Mebendazole: 100 mg b.i.d. × 3 days (see Trichuris). Pyrantel pamoate (see Ancylostoma).

Onchocerciasis

Drug	Flubendazole.[105]
Dose	750 mg IM each week × 5 weeks (for patients above 12 years of age).
Toxicity	Pain and inflammation at injection site.
Alternate drugs	Diethylcarbamazine 0.5 mg/kg t.i.d. × 3 days (max. 25 mg/day), then 1 mg/kg t.i.d. × 4 days (max. 50 mg/day), then 1.5 mg/kg t.i.d. × 4 days (max. 100 mg/day), then 2 mg/kg t.i.d. × 3 weeks (max. 150 mg/day). Followed by suramin 20 mg test dose, then 20 mg/kg IV every week × 5 weeks.
Comment	Surgical excision of worms and drainage and treatment of abscesses may also be required.

Paragonimus

Drug	Praziquantel.
Dose	60 mg/kg/day divided t.i.d. × 1 day.
Toxicity	Gastrointestinal upset. See Schistosomas.
Comment	Pediatric experience limited.[457]
Alternate drugs	Bithionol 30–50 mg/kg on alternate days × 10 (5 doses).

Scabies[373]

Drug	Gamma benzene hydrochloride.
Dose	1% Cream, lotion, shampoo. One to two applications left on 12 hours each and washed off thoroughly. Avoid eyes and mucous membrane.
Toxicity	9% absorbed. Central nervous system toxicity. Use alternate drug in infants, toddlers, and pregnancy.
Comment	Gamma benzene hydrochloride spray may be unsafe.[314]
Alternate drugs	Crotamiton: 10%; benzyl benzoate. For infants < 2 years 6% sulfur in petrolatum applied nightly × 3.

Schistosomas[276,304]

Drug	Praziquantel.
Dose	60 mg/kg/day PO, divided t.i.d. × 1 day.

Toxicity	Transient abdominal pain; dizziness; fever; malaise. headache; urticaria.
Comment	Safe in patients with glucose-6-phosphate dehydrogenase. Tablets have bitter taste. Breast milk concentrations approximate 25% of serum levels.

Strongyloides stercoralis

Drug	Thiabendazole.
Dose	25 mg/kg b.i.d. (maximum 3 g/day) × 2 days (5 days in disseminated infection).
Toxicity	Nausea, vomiting; vertigo; tinnitus; leukopenia; rash; hallucinations; seizures.[481]
Alternate drug	Pyrvinium pamoate (see Enterobius).

Taenia saginata, T. solium, D. latum, Hymenolepsis nana (tapeworms)

Drug	Niclosamide: available in U.S. from Miles Pharmaceuticals.
Dose	< 2 years: 500 mg; 2–8 years: 1 g; 8 years: 2 g, in a single dose.
Toxicity	Nausea, abdominal pain, loose stools.
Comment	Administer purgative 2 h after dose in *T. solium* infections.
Alternate drug	Paromomycin: 11 mg/kg q 15 min × 4 doses. Mebendazole. Praziquantel: 15–20 mg/kg once for Hymenolepcosis and for neurocysticer (*T. Solium*)

Toxocara	Thiabendazole: 25 mg/kg b.i.d. × 5 days (see strongyloides). Add corticosteroids for ocular toxocariasis. Diethylcarbamazine 2–4 mg/kg t.i.d. × 3 weeks is alternate.
Trichinella spiralis	Thiabendazole: 25 mg/kg b.i.d. (see Strongyloides). Corticosteroids may also reduce symptoms. Mebendazole is an alternate (see *Trichuris trichiura*).

Trichuris trichiura

Drug	Mebendazole.[224,282] Inhibits glucose uptake by parasite.
Dose	100 mg PO b.i.d. × 3 days. Single-dose treatments with 200–600 mg may also be an effective public health regimen.[211]
Toxicity	Teratogenic in rats; diarrhea, abdominal pain; headaches; dizziness; neutropenia.[259]

Alternate drug	Difetarsone (50 mg/kg/day × 5 days).[251] Tablet can be chewed or swallowed.

IV. Antiprotozoals

Babesiosis (*Babesia microti*)

Drug/Dose[527]	Quinine 25 mg/kg/day (one dose) *plus* clindamycin 20 mg/kg/day (divided q 6 h) × 7 days.
Comment	This condition is difficult to treat. The above recommendation is empiric but was successful in a few patients.[342]

Malaria[304]

Drug	Chloroquine phosphate (to treat illness). Chloroquine phosphate (to prevent infection). Primaquine phosphate (to prevent relapse after treatment) and for last 2 weeks of chemoprophylaxis after departure from area where *P. vivax* and *P. ovale* are endemic.[320]
Dose	Treatment: Chloroquine phosphate: 10 mg (base)/kg (maximum 600 mg) stat. Then 5 mg/kg q.i.d. × 2 days. Prophylaxis: Chloroquine phosphate: 5 mg (base)/kg (maximum 300 mg) once/week. Begin 1 week before travel and continue for 6 weeks after. Primaquine phosphate: 0.3 mg/kg/day (maximum 15 mg) × 14 days in a single dose.
Toxicity	Chloroquine phosphate: headache; mild visual disturbance; gastrointestinal upset; pruritus; confusion, agitation, mental disturbance.[49] Primaquine phosphate: Hemolysis in glucose-6-phosphate dehydrogenase deficient patients. Hemolytic anemia, methemoglobinema, leukocytosis (low dose), leukopenia; gastrointestinal upset.
Comment	Of primary importance for infants and children is the prevention of mosquito contact whenever possible. This may be preferable to chemoprophylaxis in young infants. *For protection against chloroquine-resistant malaria* (Eastern India, Bangledesh, South-East Africa, Central and South America, Papua New Guinea) in nonimmune children, chloroquine[320] *plus* pyrimethamine (see toxoplasmosis)/sulfadoxine (usually supplied as 25 mg/500 mg) is recommended in the following

doses given every week: ≤ 3 years: 125 mg sulfadoxine; 4–8 years: 250; 9–14 years: 375; > 14 years: 500.[28] Pyrimethamine/sulfadoxine should not be used to prevent *P. vivax* or other non falciparum forms of malaria.[341] *Treatment of chloroquine-resistant P. falciparum*: Quinine sulfate 25 mg/kg/day P.O. in 3 divided doses × 10–14 days *plus* trimethoprim/sulfamethoxazole 8 mg trimethoprim/kg/day divided b.i.d. × 5 days.[395]

or

Quinine plus pyrimethamine P.O. × 2 days: <10 kg 6.25 mg/day, 10–20 kg 12.5 mg/day, 20–40 kg 25 mg/day. *Plus* sulfadiazine: 100–200 mg/kg/day in 4 divided doses (max. 2 g) × 5 days.

Treat malaria with both chloroquine and primaquine. Primaquine not needed in congenital or transfusion malaria (no exoerythrocytic phase).

Chloroquine may turn urine orange while primaquine may cause brownish color.

Alternate drug	Quinine hydrochloride 25 mg/kg/day (max. 1800 mg/day) IV over 1 h in 2 divided doses plus trimethoprim/sulfamethoxazole × 5 days. Quinine may turn urine black.

Pneumocystis carinii[505]

Drug	Co-trimoxazole (trimethoprim/sulfamethoxazole).
Dose	*Treatment*: 20 mg/kg/day trimethoprim/100 mg/kg/day sulfamethoxazole in 4 divided doses.[192] *Prophylaxis*: 5 mg/kg/day trimethoprim/25 mg/kg/day sulfamethoxazole in 2 divided doses.[194]
Toxicity	See Trimethoprim-Sulfamethoxazole.
Alternate drug	Pentamidine isethionate.[514]
Dose	4 mg/kg IM or IV as a single dose/day.
Toxicity	Immediate reactions: hypotension, tachycardia, vomiting, hallucinations, flushing, itching (more common with IV route). Nephrotoxic (particularly when administered with other nephrotoxic drugs); abnormal liver function; hypoglycemia; rash; local reaction at injection site (pain, abscess) common.

Toxoplasma gondii[132]

Drug	Pyrimethamine.

	Sulfadiazine (or triple sulfonamides; not sulfisoxazole). Leucovorin (folinic acid).
Dose	Pyrimethamine: 1 mg/kg/day: double dose first 3 days (max. 25 mg/day) Sulfadiazine: 100 mg/kg/day in 4 divided doses. Leucovorin: 10 mg/day
Toxicity	Pyrimethamine: megaloblastic anemia; skin rash; teratogenicity[174] Sulfadiazine: See Sulfonamides.
Alternate drug	Spiramycin: 300 mg/kg/day.
Comment	Corticosteroids also recommended in ocular toxoplasmosis.

Trichomonas vaginalis

Drug	Metronidazole
Dose	15 mg/kg/day (adult dose 250 mg t.i.d.) × 7
Toxicity	See Entamoeba.

Trypanosomiasis[304]

	T. cruzi: Nifurtimox (lampit®) 5–15 mg/kg/day × 4 months. *T. brucei gambiense, T. brucei rhodesiense.* Hemolymphatic stage: suramin 20 mg/kg on days 1, 3, 7, 14, and 21. Central nervous system disease: Melarsoprol 0.36 mg/kg IV, initial dose, then increase gradually to 3.6 mg/kg at intervals of 1–5 days for a total of 9–10 doses (total 18–25 g/kg).
Alternate drug	Pentamidine: 4 mg/kg/day IM × 10 days.

V. Antivirals

Acyclovir

	A cyclic purine nucleoside active in vitro against herpes simplex, varicella zoster, and Epstein-Barr viruses.
Dose	*Topical*: 5% ointment applied with finger cot to mucocutaneous lesions q 3 h during waking hours × 7 days (duration may be longer if virus persists). *Not* for ocular use. *Parenteral*: IV 10–20 mg/kg/day divided q 8 h. Infuse over 1 h. Increase dose interval to 12 h with mild renal insufficiency and to 24 h with

	moderate dysfunction. In severe azotemia use 1/2 dose q 24 h.[327]
Toxicity	Mild local pain and stinging on application, but this may be due to tenderness of herpes ulcers. Irritation at the site of infusion. Renal function may be transiently impaired, particularly if hydration is inadequate.[327] Metabolic encephalopathy, bone marrow depression, and abnormal hepatic function have also been noted.[327] Neurologic symptoms in bone marrow transplant recipients.[499]
Comment	Useful if used early in the course of primary genital herpes simplex and for mucocutaneous herpes simplex infections in immunocompromised patients.[248] Resistance has been noted in herpes simplex virus after acyclovir therapy.[24]

Adenine arabinoside (see Vidarabine)

Amantadine

Spectrum	Influenza A.
Dose	Children 1–8 years: 5–9 mg/kg/day, given in 2 or 3 equal portions. Not to exceed 200 mg/day. Children 9–12 years: 100 mg twice daily. Children older than 12 years: 200 mg/day, given as a single dose, or 100 mg twice daily should central nervous system effects develop.
Incompatibility	Drowsiness and decreased concentration may be enhanced with chlorpheniramine.[334] Hallucinations, confusion, and nightmares with anticholinergics.[309]
Toxicity	Drowsiness; insomnia; decreased concentration; dizziness; dry mouth; headache; fatigue; allergic reaction; vomiting. Use with care in renal failure and maintain plasma concentration < 1 μg/ml.[198] Neuropsychiatric reactions, especially in patients with renal impairment. Possible increase in seizure activity. Congestive heart failure may be worsened. Hypotension; urinary retention.
Comment	Efficacy in prevention of illness estimated at 91%.[104] Treatment within 48 h of acute infection may shorten course. Excreted in breast milk—urinary retention, vomiting and skin rash has been reported in breast-fed infants.[393]

Iodoxuridine

Spectrum	Herpes simplex.
Dose	Topical (eye): 0.1% solution q 1 h in day time and q 2 h during the night. 0.5% ointment q.i.d. and at bedtime.
Toxicity	Hypersensitivity. Oncogenic and mutagenic in animals.
Comment	Herpes simplex strains resistant to idoxuridine have been described.

Trifluridine[89] (trifluorothymidine)

Spectrum	Herpes simplex.
Dose	Topical: 1% ophthalmic solution, 1 drop q 2 h.
Toxicity	Burning; palpebral edema. Punctate keratopathy. Allergy.
Comment	Mutagenic in vitro.

Vidarabine[516]

Spectrum	Herpes simplex. Varicella zoster.
Dose	Topical: 3% ophthalmic ointment q 3 h. IV: 15 mg/kg/day × 10 days (dissolve to a maximum concentration of 450 mg/liter and infuse over 12 h).
Incompatibility	Interferon may potentiate toxicity.[427]
Toxicity	Blurred vision; elevated intracranial pressure; tremors, myoclonus [especially in patients with impaired renal function;][283] burning, photophobia, local irritation; hypokalemia; inappropriate secretion of antidiuretic hormone; oncogenic and mutagenic in animals; nausea, vomiting, diarrhea; anemia, leukopenia and thrombocytopenia in cancer patients receiving high doses.[427]
Comment	Efficacious if given early in herpes simplex encephalitis.[517] May be useful in disseminated herpes simplex or varicella zoster infections in various hosts but controlled data are lacking. Of no proven usefulness against cytomegalovirus infections despite some in vitro susceptibility.

VI. Miscellaneous

Modifications of Antibiotic Doses for Oliguric Patients[36,235] *Note:* Antibiotic assay is the best way to adjust dosage in such patients. The recommendations below are based on the serum half-life after a single injection in patients with *stable* renal function. Accumulation of partially degraded active metabolites may occur with some drugs in the uremic individual.

1. If creatinine clearance is less than 10 ml/min, the patient should receive a full loading dose and then the dose at the intervals recommended below for severe renal failure.
2. Mild: creatinine clearance 50–80 ml/min.
   Moderate: 10–50 ml/min.
   Severe: < 10 ml/min.
3. Patients with lowered creatinine clearance but with normal serum urea or creatinine concentrations should be given ordinary therapeutic doses unless severe liver disease is present.

Method of Estimating Kanamycin Dosage in Renal Failure.[93] Anuria: 7 mg/kg in a single dose only. Hemodialysis: 7 mg/kg after every other dialysis. Chronic renal failure: loading dose is 7 mg/kg. Then repeat dose every third half-life. Half-life (h) = serum creatinine (mg/100 ml) × 3.

Method of Estimating Gentamicin Dosage in Renal Failure.[92] Half-life (h) = serum creatinine (mg/100 ml) × 4. Give loading dose (2.5 mg/kg) and then 2.0 mg/kg every second half-life.[446] Nomograms based on creatinine clearance and blood urea nitrogen are available to determine gentamicin dosage in renal failure,[72] but should be used with caution in children. 70% reduction in serum concentration after 12 h Kiil dialysis.[266]

Probenecid: To reduce excretion of drugs by the proximal tubules, 10–22 mg/kg/day divided q 6 h. Give ½ h before oral dose and 2 h before IV.

Transplacental Transport and Pharmacokinetics in the Newborn. See ref. 296 for review.

VII. Summary of Antimicrobial Drug Choices

Organism (gram reaction)	*Drugs of First Choice*	*Drugs of Second Choice*
Acinetobacter (−)[239]	Kanamycin Gentamicin	Tobramycin Minocycline Piperacillin
Actinobacillus (−)[187]	Chloramphenicol	Tetracycline
Actinomyces (+)	Penicillin	Erythromycin[256] Tetracycline
Aeromonas hydrophila (−)[125]	Gentamicin Trimethoprim/SMZ	Chloramphenicol Moxalactam[122]

(*Continued*)

VII. Summary of Antimicrobial Drug Choices

Organism (gram reaction)	*Drugs of First Choice*	*Drugs of Second Choice*
Bacillus anthracis (+)	Penicillin	Tetracycline Erythromycin
Bacterium actinomycetemcomitans (see Actinobacillus)		
Bacteroides (−)	Chloramphenicol[339] Clindamycin[532] Metronidazole[478]	Penicillin Piperacillin Moxalactam
Bordetella pertussis (−)	Erythromycin	Ampicillin
Borrelia	Tetracycline	Erythromycin
Branhamella catarrhalis (−)[103]	Erythromycin Cefoxitin	Tetracycline
Brucella (−)	Tetracycline ± Streptomycin	Trimethoprim/Sulfamethoxazole Kanamycin
Calymmatobacterium granulomatis (−)	Tetracycline	Streptomycin
Campylobacter fetus (−)[496]	Erythromycin	Tetracycline Gentamicin Chloramphenicol
Candida albicans	Nystatin Amphotericin B	5-Fluorocytosine Miconazole Clotrimazole-topical
Capnocytophaga (−)[144]	Penicillin Ampicillin	Erythromycin Carbenicillin
Chlamydia	Tetracycline Erythromycin	Chloramphenicol Sulfonamide
Clostridia (+)[474]	Tetracycline Penicillin Metronidazole	Erythromycin Chloramphenicol
Clostridium difficile (+)[110]	Vancomycin Metronidazole	Penicillin Ampicillin
Corynebacterium diphtheriae (+)	(antitoxin) Erythromycin	Penicillin
Enterobacter (−)	Gentamicin Tobramycin	Ticarcillin Polymyxin-topical Cephalosporin Amikacin
Erysipelothrix (+)	Penicillin	Tetracycline
Escherichia coli (−)	Gentamicin Tobramycin	Ampicillin Polymyxin-topical Cephalosporin Kanamycin
Flavobacteria (+)	Trimethoprim/Sulfamethoxazole[1] Cefoxitin	Rifampin (combined with another drug) Clindamycin

VII. Summary of Antimicrobial Drug Choices

Organism (gram reaction)	*Drugs of First Choice*	*Drugs of Second Choice*
Francisella tularensis; see Yersinia		
Fusobacterium	Penicillin	Metronidazole Clindamycin Chloramphenicol
Gardnerella (Haemophilus) *vaginalis*	Metronidazole (for vaginitis)	Ampicillin
Granuloma inguinale; see Calymmatobacterium		
Haemophilus ducreyi[171]	Trimethoprim/ Sulfamethoxazole[140]	Tetracycline Rifampin Erythromycin
Haemophilus influenzae (−)	Ampicillin Chloramphenicol	Moxalactam Cefotaxime Tetracycline Sulfonamide
Haemophilus aphrophilus *Cardiobacterium hominis* *Eikenella corrodens*	Penicillin	Chloramphenicol Tetracycline
Hafnia; see Klebsiella		
Klebsiella (−)	Gentamicin Tobramycin	Cephalosporin Chloramphenicol Kanamycin Polymyxin-topical
Legionella pneumophila[262]	Erythromycin	Rifampin Gentamicin
Leptospira	Penicillin	Tetracycline
Listeria monocytogenes (+)	Ampicillin Kanamycin Ampicillin + Gentamicin or Amikacin	Penicillin Tetracycline Erythromycin Chloramphenicol
Moraxella (−)	Gentamicin	Tetracycline Cephalothin
Morganella morgani (−)	Kanamycin Gentamycin Tobramycin	Cephalosporin Amikacin Chloramphenicol Ticarcillin
Mucor	Amphotericin B	
M. tuberculosis	INH Rifampin Ethambutol	Streptomycin PAS Cycloserine Ethionamide Pyrazinamide

(*Continued*)

VII. Summary of Antimicrobial Drug Choices

Organism (gram reaction)	*Drugs of First Choice*	*Drugs of Second Choice*
Mycobacteria, atypical	INH + Rifampin ± Ethambutol	Erythromcyin Streptomycin PAS Cycloserine
Mycobacterium fortuitum	Amikacin Cefoxitin	Rifampin Doxycycline
Mycobacterium marinum[191,431]	Trimethoprim/Sulfamethoxazole[398] Amikacin Kanamycin	Rifampin + Ethambutal Tetracycline[502]
Mycobacterium leprae	Dapsone ± Rifampin	Acedapsone Clofazimine
Mycoplasma pneumoniae	Erythromycin	Tetracycline
Neisseria gonorrhoeae (−)	Tetracycline[306] Penicillin Amoxicillin	Spectinomycin Cefoxitin
Neisseria meningitidis (−)	Penicillin	Ampicillin Chloramphenicol Sulfonamide
Nocardia (+)[167]	Trisulfapyrimidines Trimethoprim/Sulfamethoxazole Minocycline	Sulfonamide + agent chosen by sensitivity tests, Amikacin Cycloserine
Pasturella multocida (−)	Penicillin	Tetracycline
Pneumocystis carinii[193]	Trimethoprim/Sulfamethoxazole[192]	Pentamidine isethionate
Propionibacterium acnes[98]	Penicillin	Erythromycin Tetracycline Cefotaxime
Proteus mirabilis (−)	Ampicillin Gentamicin Tobramycin	Kanamycin Cephalosporin Chloramphenicol Ticarcillin
Proteus vulgaris (−)	Kanamycin	Cephalosporin
Providencia rettgeri (−)	Gentamicin Tobramycin	Amikacin Chloramphenicol Ticarcillin
Providencia spp. (−)	Kanamycin Amikacin	Ticarcillin Gentamicin Cephalosporin
Pseudomonas aeruginosa (−)	Ticarcillin ± Tobramycin or Gentamicin	Amikacin Piperacillin Polymyxin-topical

VII. Summary of Antimicrobial Drug Choices

Organism (gram reaction)	*Drugs of First Choice*	*Drugs of Second Choice*
Pseudomonas pseudomallei (−)	Minocycline Tetracycline	Trimethoprim/Sulfamethoxazole
Pseudomonas cepacia	Trimethoprim/Sulfamethoxazole	Chloramphenicol
Pseudomonas mallei	Streptomycin + Tetracycline	Chloramphenicol + Streptomycin
Pseudomonas maltophila[535]	Gentamicin + Carbenicillin + Rifampin	Trimethoprim/Sulfamethoxazole[134]
Rickettsia	Chloramphenicol	Tetracycline
Salmonella (−)	Ampicillin Amoxicillin	Chloramphenicol Cephalosporin Trimethoprim/Sulfamethoxazole
S. typhi (−)	Chloramphenicol Ampicillin	Trimethoprim/Sulfamethoxazole
Serratia (−)	Gentamicin Tobramycin	Ticarcillin Carbenicillin Chloramphenicol Cephalosporin
Shigella (−)	Ampicillin	Trimethoprim/Sulfamethoxazole Tetracycline
Spirillum minor (−)	Penicillin	Tetracycline Erythromycin
Sporothrix schenckii	Iodine	Amphotericin B
Staphylococcus (+) resistant to penicillin	Methicillin Nafcillin Dicloxacillin Cloxacillin	Cephalosporin Erythromycin Clindamycin Vancomycin
Staphylococcus (+) resistant to methicillin	Vancomycin ± Rifampin	Rifampin + Gentamicin[271]
Staphylococcus (+) sensitive to penicillin	Penicillin	Erythromycin Clindamycin
Streptobacillus moniliformis (−)	Penicillin	Tetracycline Cephalosporin Vancomycin
Streptococcus including pneumoniae (+)	Penicillin	Erythromycin Cephalosporin Ampicillin Clindamycin
Streptococcus group B (+)	Penicillin Ampicillin	Chloramphenicol Penicillin *or* Ampicillin + Gentamicin *or* Amikacin

(*Continued*)

VII. Summary of Antimicrobial Drug Choices

Organism (gram reaction)	*Drugs of First Choice*	*Drugs of Second Choice*
Streptococcus faecalis group D (enterococcus) (+)	Penicillin + Streptomycin Ampicillin + Kanamycin or	Vancomycin + Streptomycin[513]
Streptococcus bovis group D (+)	Penicillin	Erythromycin[485] Cephalosporin
Treponema pallidum	Penicillin	Cephalosporin Erythromycin Tetracycline
Vibrio cholerae (−)	Tetracycline	Trimethoprim/Sulfamethoxazole
Yersinia enterocolitica (−)	Trimethoprim/Sulfamethoxazole Kanamycin	Sulfonamide Tetracycline
Yersinia pestis or *F. tularensis* (−)	Tetracycline Chloramphenicol	Streptomycin Gentamicin

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3

Infections of the Newborn

General Considerations

Newborns are special! They are exposed to several diverse environments during their intrauterine, perinatal, and postnatal lives. Because of this, and their relatively immature state of physical and immunological development, they have infectious disease problems that deserve special emphasis. In fact, there are textbooks exclusively devoted to infectious diseases of the fetus and newborn. Do not worry, this chapter will not attempt to be comprehensive in every detail, but rather focus on the commonest problems.

Newborn Environments (Fig 3-1)

The first world the fetus encounters is unique in several aspects.

Intrauterine. The ideal isolation room—or is it? There is no problem with airborne infection and direct contact with infected persons is impossible. Maternal immunity is altered so that tolerance is pronounced, allowing the fetus to persist without immunologic challenge, in most cases. Contact between the mother's environment and the fetus is maintained and controlled via the placenta and umbilical cord, which are generally effective in limiting in utero antigenic exposure of the fetus. Nevertheless, breakthroughs occur. A common example is congenital cytomegalovirus infection, probably the most frequent congenital infection. Other maternal infections in the first trimester (e.g. influenza, measles, tuberculosis, etc.) have been associated with abortion and fetal death. These severe outcomes may be nature's way of avoiding horrendous congenital anomalies. In fact, these infections can be likened to lethal mutations, since they occur so early in embryonic development.

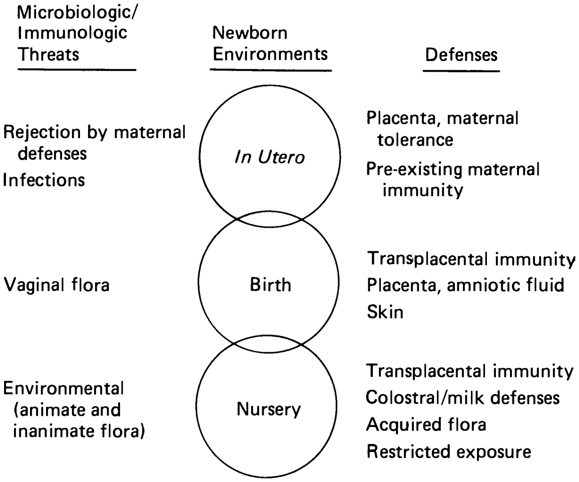
Microbiologic/ Immunologic Threats
Newborn Environments
Defenses
Rejection by maternal defenses
Infections
In Utero
Placenta, maternal tolerance
Pre-existing maternal immunity
Vaginal flora
Birth
Transplacental immunity
Placenta, amniotic fluid
Skin
Environmental (animate and inanimate flora)
Nursery
Transplacental immunity
Colostral/milk defenses
Acquired flora
Restricted exposure

Figure 3-1. Summary of risks of infection and defense mechanisms involved at various stages of the infant's development.

In the second and third trimesters the environment seems to offer better protection to the fetus, as abortions become less common even in the face of similar infectious disease exposures. This is probably due to improved ability of the mother's placenta to protect the fetus from infection and, more importantly, to the fetus' more advanced development and maturing defense mechanisms. In fact, differentiation of the immune system begins in utero during the eighth to twelfth weeks of gestation and the fetus is capable of specific immune responses, including production of IgG, from the twentieth week of gestation.[50,337]

In the third trimester the environment continues to protect as long as the amniotic membranes are intact and the mother remains reasonably healthy. Although these membranes normally maintain the amniotic cavity in a sterile condition, they are not absolutely impermeable barriers and the fluid may become colonized by vaginal flora in some circumstances, even if the membranes are apparently intact.[328] The other portal of entry to this environment is via the fetus. Thus, systemic maternal infection transferred to the placenta and to the fetus (e.g., rubella, cytomegalovirus, etc.) can then seed the amniotic fluid by shedding or excretion from the fetus. These viruses have occasionally been recovered by amniocentesis in the third trimester.[110]

Birth. The big event! An abrupt change in the infant's environment occurs at the time of birth. Amniotic membranes rupture and the infant is precipitously exposed to vaginal, perineal, and environmental flora. Suddenly he must cope with a variety of organisms, which occasionally include serious invaders such as group B Streptococcus, *Escherichia coli*, and Staphylococcus. Occasionally we add to the risk of infection by birth trauma (e.g., lacerations and cephalohematoma) and fetal monitoring devices.[7]

The newborn's bacterial flora initially colonizes the skin and mouth and is acquired from the maternal genital tract.[169] It is not unusual to see *Candida albicans* or *Streptococcus agalactiae* (group B) in these sites in the infant when the mother is colonized with these organisms. Patterns of colonization vary considerably depending on characteristics of the mother (i.e. maternal vaginal flora), obstetric and newborn units (i.e. environmental flora, crowding), breast-feeding, use of antibiotics (i.e. selection of resistant bacteria), and bathing and cord-care practices. For example, castile soap has little effect on *S. aureus* or gram-negative bacterial colonization, while triple dye is highly active against staphylococci but is less effective against group B streptococci and gram-negative bacteria than silver sulfadiazine.[43,410]

Generally, *Staphylococcus epidermidis* colonizes the skin, and a mixture of aerobes (*Streptococcus viridans*) and anaerobes (most cocci) colonize the mouth and then the upper respiratory and gastrointestinal tracts.[7,69] The umbilicus is frequently colonized by *Staphylococcus aureus*. In one study of normal breast-fed newborns, 22% were colonized by *S. aureus* at that site on the first day of life and 87% by the sixth.[372] In breast-fed infants the predominant fecal organisms by the first week of life are anaerobes including bifidobacteria, Bacteroides, and clostridia; enteric bacteria and enterococci are also common. In bottle-fed babies, *E. coli* and Lactobacillus predominate.[481] Infants born by cesarean section may acquire maternal flora more slowly and may be prone to acquire the flora from the nursery environment as well.

Maternal genitourinary colonization with *Mycoplasma hominis* and *Ureaplasma urealyticum* may spread to the newborn,[396] and occasionally cause disease,[400] but much remains to be learned about these pathogens in the perinatal period.[436,437]

Premature newborns in intensive care nurseries are frequently exposed to antibiotics. They have little bacterial colonization for the first few days and thereafter acquire a mixed flora including gram-negative pathogens.[413]

The Nursery. This new world consists of many different environments. First consider the normal newborn. He is in a relatively pathogen-free environment in the normal newborn nursery and at home. He is protected in most circumstances from contact with individuals with obvious infectious diseases and seldom exposed to antibiotics. Acquired respiratory viral infection is probably the most common infectious threat in these environments and can be limited by careful screening of the infant's contacts. Contrast this with the ill newborn admitted to the intensive care unit. This is a more densely populated area, with pathogenic microorganisms carried not only by nursery mates, but also by staff, and on surfaces and equipment.[56,138] Crowding, low caretaker/patient ratio, poor ventilation, use of antibiotics, and underlying medical and surgical conditions are all factors that increase the likelihood of abnormal colonization and infection in these newborns.[167] The nosocomial infection rate in many of these units is among the highest in the hospital. Rates of 20–30% are not unusual, and often include outbreaks of infection that spread rapidly through this closed population.[211] Frequent causes are *S. aureus*, Enterobacteriaceae, and respiratory and gastrointestinal viruses.[100,106]

Immunity

Newborns are immunologically immature, development of host defenses being directly related to gestational and postnatal age. Almost all immunologic parameters measured are relatively reduced in newborns when compared with adults.[310] Thus, although the ability to produce immunoglobulins is present, the speed and magnitude of this humoral antibody response are lower than in older children.[2] IgA is the least developed response among the humoral globulins, an adaptation possibly related to the role of maternal breast milk in supplying gastrointestinal and respiratory defenses via colostral and milk IgA and other immunoglobulins of this class passively transferred to the infant.[166] The more prevalent the communicable enteric and respiratory infections are in the community, the more useful is breast-feeding as a preventive modality.[335]

The humoral immune compartment is relatively deficient in complement,[472] the alternate complement pathway,[312] and immunoglobulins. Many of these act as opsonins or enhancers of phagocytic function. Their subnormal function compounds the other abnormal features of newborn phagocytes: adherence,[250] deformability, chemotaxis, phagocytosis, and microbicidal activity.[386,394,442] These deficiencies also involve the resting macrophage system, and are affected by the route of delivery of the newborn.[152] The net effect of this immunologic immaturity is an increased susceptibility to infection. For example, newborn animals are less resistant to experimental herpes simplex infection than adults, a susceptibility that can be reversed by injections of adult peritoneal macrophages before infection.[144,227]

Cell-mediated immune functions are also undergoing dramatic changes in the newborn. Initially, suppressor T-cells predominate and the infant's immune system is tolerant, like his mother's. They are then replaced by stimulator (helper) T-cells, which enhance both B- and T-cell responses.[313]

Female newborns are less commonly infected and recover more readily than males. Immunoregulatory genes on the X chromosome may be partly responsible by contributing to higher IgM concentrations and better humoral responses of female infants.[359]

Consideration of the immune defenses of the newborn is incomplete without some appreciation of anatomic defenses. The infant has less temperature control, less well-developed nasal and sinus systems, and an immature mucociliary system. His growth is at a rapid stage and seems particularly susceptible to colonization and invasion by certain pathogens, such as *Listeria monocytogenes*, group B streptococci, Chlamydia, and Staphylococcus. The umbilical stump may provide a ready entry point for bacterial invasion in normal newborns. In others, there may be abnormal sites created iatrogenically, e.g., by circumcision, heel sticks, endotracheal tubes, catheters, etc. Avoiding these hazards is only one of the factors that prevent infection in this highly susceptible host (Table 3-1).

Clinical Manifestations

In addition to particular environmental exposures and immature immunity, a newborn is peculiar in his clinical responses to infectious diseases. Thus the signs of infection are often nonspecific, e.g., irritability, poor feeding, abnormal tone, poor temperature control, acidemia, apnea, jaundice, etc. Because of the nonspecific nature of these signs and the seriousness of newborn infections, sepsis is widely, but appropriately, overdiagnosed and overtreated in the newborn.

Thus the newborn is a special person. His environments are different, his immunity is different, and he manifests infectious diseases in a nonspecific fashion. It is no wonder some consider the study of neonatal infectious diseases a separate specialty.

Congenital and Perinatal Infections

Cytomegalovirus

Epidemiology. Cytomegalovirus (CMV) is the most frequently recognized congenital infection and the most common infectious cause of mental retardation. The incidence of CMV infections varies considerably. In North American populations virus is present in cervical secretions and urine of approximately 5% of mothers in the third trimester, and is also present in breast milk and in semen.[136] A much smaller percentage of newborns acquire virus (estimated 0.2–8%). We recently encountered

TABLE 3–1. Factors Involved in Protecting Newborns from Infection in Early Infancy

Maturation of host defenses and acquisition of normal flora
Control of exposure to pathogens (hygiene/contacts)
Avoidance of predisposing factors (prematurity, surgery)
Transplacental immunity
Breast milk

five newborns during 6 months with symptomatic congenital CMV infection.[264] In contrast, Larke et al. reported only four symptomatic newborns among the 64 congenitally infected subjects detected in a survey of 15,212 births during a period of 44 consecutive months.[260] These data are reminiscent of those reported for carriage, colonization, and infection rates with several well-known bacterial pathogens as well, e.g., Streptococcus group B, *E. coli,* and *S. aureus.*

This DNA virus is a member of the herpesvirus group and is often present in a latent form or is asymptomatically excreted by seropositive subjects. The exact site of latency is unknown, but thought to be in blood leukocytes. Blood containing antibody to CMV should be considered infectious. In fact, congenitally infected infants continue to excrete virus despite the presence of high antibody titer.[158] Since transfusion-acquired CMV disease (hemolysis, hyperbilirubinemia, and hepatosplenomegaly) can be a problem for newborns and immunosuppressed hosts, it is advisable to test newborns for CMV antibodies and transfuse only appropriately matched blood.[9] Alternatively, CMV-antibody negative, or frozen, deglycerolyzed erythrocytes may also carry less risk of posttransfusion CMV infection.[441] Posttransfusion-infected infants may be a source of infection for their mothers as well.[475] Antibody may be present in up to 50% of North American women during their fertile years, in 90–100% of mothers in developing countries, and in young unmarried women with many sex partners. In fact, mothers of infants excreting CMV are predominantly young, unmarried, and poor.[259] Most commonly, the virus is excreted in the urine, cervical secretions, semen, and breast milk.[126] Opportunities for venereal spread are frequent. Although primary maternal infection during the first and second trimesters are of most concern, symptomatic congenital infection has also been documented after reactivation of infection in the mother.[10]

Clinical Manifestations. When CMV is acquired during pregnancy, the effects are variable. Primary infection with a large number of viruses at a critical stage of fetal development causes the most severe consequences. Early in pregnancy this might be abortion, and later, severe congenital anomalies (Fig. 3–2). Although congenital infection has been reported in the offspring of mothers who had previous humoral immunity to CMV (reactivation), these infants do not usually have symptomatic disease.[418]

The outcome of symptomatic congenital CMV infection is grave. A group of 33 such patients were followed for a mean of 4 years (9 months–14 years).[343] Ten died and 21 had neurologic or auditory handicaps. Microcephaly and mental retardation were present in 70 and 61%, respectively. The future is much brighter for normal newborns found to be asymptomatically excreting CMV, although 10–20% may have intellectual or perceptual deficits.[199,420] Thus, it appears that reactivation (or superinfection) during pregnancy is less hazardous to both the mother

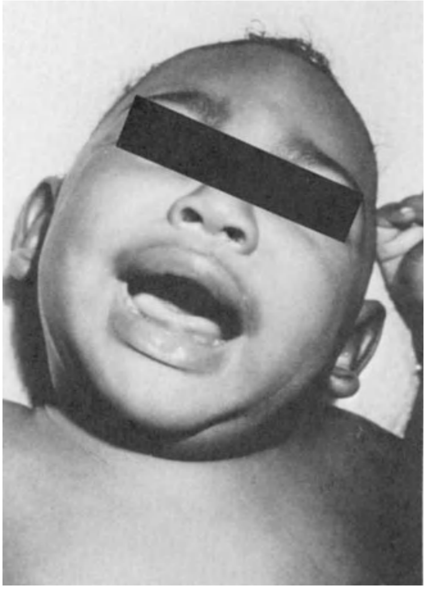

Figure 3–2. Severe microcephaly in a newborn with congenital cytomegalovirus syndrome.

and the infant than primary infection. Alas, it is not that simple. It is becoming apparent that there is considerable antigenic variation among different isolates of CMV.[458] It is possible that immunity is more strain-specific than we had previously imagined and that reactivation may actually represent infection with an antigenically different virus. This may explain the rare occurrence of congenital CMV infection in consecutive offspring.[137] Long-term followup studies and reanalysis of many seroepidemiologic observations are necessary in light of these findings.

The classic features of severe congenital CMV infection include microcephaly and intracranial calcifications (Table 3–2). The infant may be small for gestational age and/or premature, but this is not seen in all

TABLE 3–2. Congenital CMV Infection

Microcephaly
Periventricular calcifications
Hepatosplenomegaly
Jaundice
Pneumonia
Petechiae
Deafness
Chorioretinitis
Optic atrophy

cases. Other common features of this syndrome can also be seen in several of the other congenital virus infections to be discussed below. These are hepatosplenomegaly, jaundice (often with a predominant direct component), thrombocytopenic purpura, and chorioretinitis.[340] Other eye problems include microphthalmia; optic nerve hypoplasia; and atrophy, coloboma, and cataracts.[154] These abnormalities are usually noted within the first 48 h in severely affected infants. Others have hepatosplenomegaly, hyperbilirubinemia, and thrombocytopenia in the first or second week of life. In both cases the infant is usually excreting large amounts of virus in the urine and smaller amounts are present in the throat. Inguinal hernias in males and dental enamel hypoplasia have also been reported.[419]

Diagnosis. If freshly inoculated into tissue culture, cytopathic evidence of this virus is often present within 24–72 h. More rapid diagnosis can be made by examination of the urine by electron microscopy and visualization of herpes group virus particles.[267] Examination of the placenta for histopathologic evidence of villitis or chorioamnionitis, intranuclear and intracytoplasmic inclusion bodies, giant cells, and/or CMV antigen detected by immunofluorescent staining are useful procedures as well (Fig. 3–3). If positive, they can provide early clues to the diagnosis of congenital CMV. Some cases of congenital infection may also be suggested by the presence of IgM specific antibody in cord serum, a finding that also implies a poor prognosis.[176]

Postnatal Infection. Acquired CMV infection can also cause lymphadenitis or infectious mononucleosis in early infancy and later life.[36] A syndrome of pneumonia, hepatosplenomegaly, and atypical lymphocy-

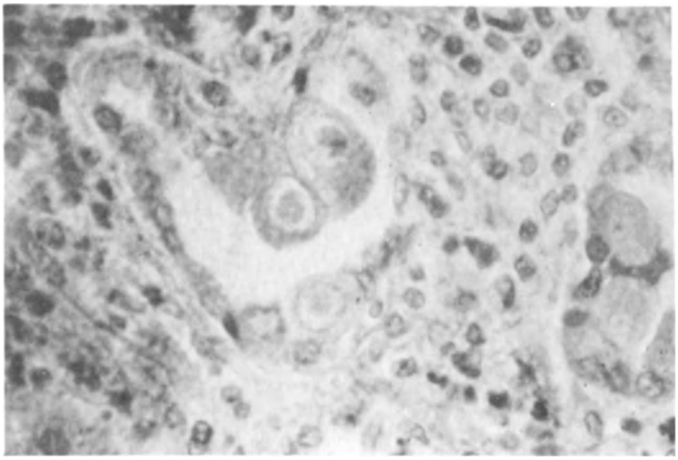

Figure 3–3. Cytomegalic inclusion bodies in lung of a congenitally infected newborn.

tosis has also been reported in infants, with CMV the culprit; this may also be transfusion-related,[197] but is most likely to be acquired via breast milk or maternal secretions in small premature infants with seropositive mothers.[477] In addition, CMV has been implicated as a component of mixed infection in the lung, e.g., with *Pneumocystis carinii* and *Chlamydia trachomatis*.[48] Day-care centers may be a frequent source of postnatally acquired CMV infections, the vast majority of which are asymptomatic.[342]

Prevention and Therapy. The diagnosis of this congenital infection is important for prognostic reasons, to determine the frequency and emphasis of followup, for genetic counseling, and, hopefully, for specific therapy in the future. Although vaccines[198] and antiviral therapy[412] are under study, neither approach appears imminently successful at this time. Isolation of infected newborns is important to prevent spread of virus to susceptible contacts;[411] precautions when contacting wounds, skin, and oral surfaces (Chapter 13) are recommended since virus is present in urine, saliva, and breast milk[124] and spread by direct contact. Nosocomial, nonparenteral spread was recently reported in four infants in a neonatal intensive care unit, two of whom died.[182] Pregnant individuals should be particularly careful to avoid contact with these babies. Personnel working in newborn, transplantation, and oncology units should be tested serologically. If susceptibility is demonstrated (e.g., by lack of fluorescent antibody), extreme caution is urged during pregnancy. Both primary and recurrent CMV infections have been associated with congenital infection, and indications for termination of pregnancy after primary maternal infection are unclear.[345]

Congenital Rubella

Epidemiology/Pathogenesis. Maternal infection with rubella virus can be disastrous for the developing fetus. The danger period begins 2–3 weeks before implantation and is maximal (up to 80% congenital infection) in the first 12 weeks of pregnancy.[309] The earlier the infection occurs, the more likely it is that the fetus will be seriously injured. Maternal infection after the first trimester may still result in mild neurologic defects manifest as learning and cognitive disabilities.[200] Most of these maternal infections are primary, but late-onset congenital rubella syndrome has also been described after reinfection during pregnancy.[271]

If the mother is infected with rubella before or around the time of conception, the consequences are probable interference with implantation, markedly abnormal cell division in the young embryo, and abortion. The mother may be unaware of these events. Rubella in the first 6 weeks of gestation results in cataracts, congenital heart disease (especially lesions of the pulmonary arterial system and patent ductus arteriosus), and deafness in the majority of infants.[205] Often these defects are present at birth or shortly thereafter, however deafness may not be appreciated early on but may become obvious during the first 2 years of life.

Clinical Manifestations. Consequences of rubella in the fetus are diverse and reflect viral infection of many tissues (Table 3–3). Jaundice, hepatosplenomegaly, thrombocytopenia, cataracts, and deafness are common (Fig. 3–4). Defects range from impairment of the cell-mediated immune system[77] to multiple endocrinopathies[78,162,357,483] and hematologic abnormalities.[314] Growth retardation, which is often reflected by small stature in later life, may be due to inhibition of cell division in the most rapid developmental stages, but may also reflect growth hormone deficiency.[269,357] Similarly, both generalized hematologic depression and autoimmune hemolytic anemia have been reported.[314]

Decreases in antibody titer and failure to respond to booster immu-

TABLE 3–3. Possible Newborn Consequences of Maternal Rubella Infection During Pregnancy

Age of Newborn at Onset of Signs of Congenital Infection

- Early (0–1 month)
  - Growth retardation
  - Congenital heart defects
  - Deafness
  - Cataracts
  - Thrombocytopenia
  - Hepatosplenomegaly
  - Chromosomal abnormalities[21]
  - Osseous lesions (mostly metaphyseal)[388]
  - Jejunal atresia[139]
  - Renal anomalies[305]
  - Hypoplasia of aorta[399]
- Late (1–6 months)
  - Interstitial pneumonia
  - Skin rash[292]
  - Diarrhea
  - Hypogammaglobulinemia
- Very late (months-years)
  - Progressive encephalitis[444]
  - Diabetes mellitus
  - Thyroiditis
  - Myxedema[27]
  - Growth hormone deficiency
  - Enamel defects in deciduous teeth[179]
  - Glaucoma[59]
  - Loss of rubella antibody[101]

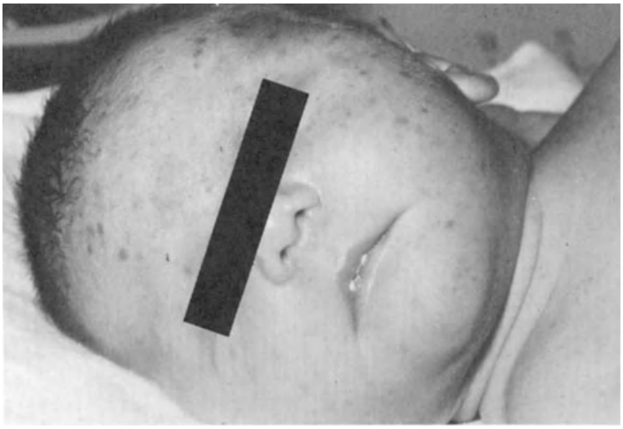

Figure 3–4. Congenital rubella. Note jaundice and petechiae.

nization have been reported in 18% of children with congenital rubella who reached their fifth birthdays.[101] It is unclear whether this represents immune tolerance or merely reflects a lack of sensitivity of the rubella serologic test. Interplay of genetic and infectious etiologies is witnessed by the fact that the children with congenital rubella syndrome who develop early-onset diabetes mellitus have an increased prevalence of HLA antigens DRw3 and DRw4, which are classically associated with diabetes in other children.[162] These children also have increased levels of circulating islet cell antibody, probably reflecting injury to pancreatic cells by rubella virus. Some of the very late congenital rubella manifestations (which occur from 3 to 10 years of age) have been thought to be due to autoimmune phenomena documented, in part, by the detection of circulating immune complexes.[434] Whether this is cause or effect is not clear.

Neurologic sequelae can be extremely variable (e.g., gross mental retardation and aqueductal stenosis).[382] Some children have major neurologic impairment in early infancy. In others, motor delays and poor balance and coordination become evident in the first 2 years of life. In still others, behavior problems, learning deficits, and progressive hearing loss can develop at up to 10 years of age;[116] some of these children may have progressive rubella panencephalitis, a syndrome characterized by spasticity, ataxia, intellectual impairment, and chronic brain changes similar to those described in subacute sclerosing panencephalitis due to measles.[443] An immune pathogenesis has been suggested, partly supported by the demonstration of immune complexes in the serum and cerebrospinal fluid (CSF) of two patients.[105]

Diagnosis. Culture of rubella virus from amniotic fluid or fetal specimens is diagnostic, although rarely obtained.[270] Postnatally, rubella virus is present in the infant's throat and urine for months and even years.[393] Virus can also be found within tissues years after congenital infection.[304] Three to five days, and occasionally longer, may be required for virologic diagnosis.

Serologic evidence of infection is usually obtained by comparing the hemagglutination-inhibition antibody in the mother's and the infant's sera at the time of birth. Congenital rubella is suggested if the newborn's sera has a titer fourfold or greater than the mother's or if both have high titers. If the infant's antibody is predominantly of the IgM class, this is also presumptive evidence of congenital infection, particularly if the presence of rheumatoid factor is ruled out.[446]

Prevention. Although much effort has been spent in the development of rapid tests for this diagnosis in the newborn, it seems an unfortunate emphasis. There is little one can do to prevent the destructive effects of rubella virus. The diagnosis should be suspected on the basis of knowing the seroimmune profile of the mother well before birth. Armed with this information, the physician will be in a much better position to detect infection during pregnancy or to immunize the mother in the immediate postpartum period. Although this procedure has occasionally led to acquired rubella in the newborn, the disease is mild if acquired postnatally.[259]

The risk of rubella vaccination around the time of conception deserves comment. Vaccine manufacturers recommend avoiding conception for 3 months after immunization with rubella virus. Some of the early vaccine strains were shown to infect the placenta and were even cultured from aborted products of conception. The RA 27/3 vaccine currently available in the United States is apparently much less teratogenic than previous vaccine strains. Despite careful followup of 15 pregnant women who inadvertently were vaccinated with this vaccine strain during the first trimester of pregnancy, all offspring were normal and no virus could be recovered from infants or other tissues.[82] Thus, accidental vaccination with RA 27/3 rubella vaccine during pregnancy is not an indication for therapeutic abortion. Similarly, spread from vaccinee to contacts is of very little consequence. There is no problem, therefore, in vaccinating young children whose mothers or schoolteachers may be pregnant.[147]

I hope the above discussion becomes one of historical interest in the coming years, considering the preventability of this condition. Adequate rubella immunization of the young female population before conception combined with careful serologic screening programs can with rare exception prevent congenital rubella.[341] Standard gynecologic and obstetric care should include rubella screening and immunization. In many communities, pediatricians, family practitioners, and generalists have taken the lead and are stimulating efforts to strengthen serologic screening and rubella immunization procedures for girls approaching puberty. Rubella vaccines are well tolerated and provide long-standing immunity. Our challenge is to use them effectively.

Congenital and Perinatal Herpes Simplex Infections

Herpes simplex virus is closely related to another DNA virus, CMV, in many of its characteristics, including its propensity for latency, reactivation, and genital and congenital infection. Some feel these are "sister" viruses—a good sister in some respects and an evil one in others. For example, herpes simplex is less likely to invade the maternal bloodstream and induce placentitis and gross fetal abnormalities; however, if acquired during or shortly after birth, infection often may be fatal. Defective antiviral cellular immunity appears to be a major factor determining the severity of these infections in newborns.[248]

Clinical Manifestations: Adult. Herpes simplex infection in the adult is manifest mainly as mucocutaneous lesions in and around the mouth and eyes due to type 1 virus, and genital lesions due to type 2. These are usually vesicles or shallow ulcers and are recurrent in many patients. Primary herpetic infection in the mother seems most dangerous to the developing fetus. This is likely to be due to type 2 virus since the majority of primary type 1 infections occur in preschool or young children, many of whom are asymptomatic. Primary type 2 infections are generally associated with sexual activity.

Congenital Infections. Herpes simplex virus infection can invade the mother's bloodstream, placenta, and fetus.[15] This may result in abortion in the first trimester and, occasionally, congenital malformations similar to those seen for the more classic teratogenic viruses.[148,349] Thus, gross neurologic abnormalities, chorioretinitis, and, occasionally, hepatosplenomegaly and hematologic abnormalities have been reported. Both abortion and congential abnormalities are seen much less frequently than with CMV or rubella.

Neonatal Infection: Epidemiology. Active herpes simplex infection in the mother's genital tract or perineum, and much less rarely at other sites in the body, poses a serious threat to the newborn.[67,149] Perinatally acquired infection may occur with intact fetal membranes.[185] Although maternal genital infection is the most common source, the virus may occasionally be acquired via breast milk (the highest risk is probably in primary maternal infection,[122] fetal-monitor scalp electrodes,[165] and from other infants, mothers, and personnel).[149,274]

Maternal genital infection may consist of primary or recurrent lesions, although the story is not clear in this respect. Originally it was thought that primary infections were most important, and that the newborn who did not acquire immunity from the mother would be at highest risk. The presence of serum neutralizing antibody has recently been correlated with herpesvirus neutralization by amniotic fluid, which may partly explain the rarity of perinatal herpesvirus infections despite the frequency of maternal infection.[66] Then evidence seemed to point against the validity of this theory, as preexisting antibody, indicating prior infection with herpesvirus, was found in some infected infants, and seemed to offer little protection against progressive infection. The plot thickened when different types of herpesvirus were described, leading to new speculation that type-specific antibody might be critical. Now we are becoming aware of strain differences among viruses of the same type. This is a consequence of specific DNA nucleotide sequences contained in each herpesvirus.[190] There may be enough strain-to-strain specificity to explain the presence of antibody in some of the infants without protection. My own bias is that recurrent infection with an identical strain is unlikely to invade and progress in the newborn since the mother will have had considerable exposure to this strain and should have transmitted some immune protection to her offspring.[454] A new strain, although of the same type, would present an intermediate risk to the newborn. A new type of herpesvirus would present the highest risk, particularly in subjects without prior infection with either type. Considering the complexity of the problem and the theoretical nature of these comments, the safest course would be to assume that all herpes simplex viruses, when present, pose a risk to the fetus and newborn. Thus, special precautions and interventions may be required (see Treatment below).

Diagnosis. Herpes simplex infections are relatively easy to diagnose. It is one of the fastest growing and hardiest viruses around. Most virus laboratories can give the clinician an answer within 24–48 h, if the specimen is rapidly transported and inoculated into fresh tissue culture of epithelial origin. Use of cotton swabs stored at refrigerator temperature is best if any delay is anticipated.[55] The diagnosis can also be made by serologic means, and is suggested by Papanicolaou smear, examination of the placenta, and direct fluorescent antibody examination of epithelial cells from the infant or the mother.[15] Unfortunately, Papanicolaou smears miss about one-quarter of virus-positive cases.[67] Examination (Tzanck) of the base of a vesicular lesion may show giant cells and intranuclear inclusions, also hallmarks of herpes simplex infections. These are difficult to see and their absence cannot be relied upon to rule out the diagnosis. Central nervous system (CNS) or visceral infection without skin lesions usually requires biopsy for early diagnosis, although glycoprotein antigen excretion may provide a noninvasive, albeit indirect, diagnostic test in the future.

The infected mother or father and newborn can often be recognized by the presence of skin vesicles.[180] At other times, it is not so easy.[4] The usual scenario related to herpes simplex infections in newborns takes place in the peripartum period. The mother may have recurrent or primary herpes genitalis in the third trimester. The alert obstetrician is aware of the risks in newborns and considers some intervention. The best way to handle this is to culture prospectively the site of infection in the mother during this trimester. If labor begins while the mother is still excreting virus, the infant should be delivered by cesarean section and an attempt made to interrupt direct contact between mother and infant for at least a 4- or 5-day period. Then, if the mother is still excreting virus, specific advice should be based on viral cultures and neutralizing antibody studies of the infant and the mother. Whatever the decision, mother should be cautioned to use scrupulous hygienic technique to prevent spread by direct contact.[67,241]

Neonatal Infection: Clinical Manifestations. Infection in the newborn may take many forms and occur any time during the first month of life (average 16 days). This ranges from isolated skin lesions to disseminated infection. Unfortunately, the latter may occur without any mucocutaneous lesions.[25] Skin lesions may be single or diffuse and even zoster-like.[325] They may remain localized in some of these infants, and recurrent skin lesions are common.[215] Progression of the disease from isolated skin lesions occurs in approximately 70% of infants.[468] Dissemination often involves lungs,[175] liver (metabolic effects may include hyperammonemia),[41] spleen, and CNS including eye (chorioretinitis). Conjunctivitis and keratitis may be present as part of generalized infection, or as the only site of involvement.[13] The virus can frequently be isolated from the CSF in these cases and, even more frequently, from infants with localized CNS infection. Mortality in herpes neonatorum may be as high as 60% and at least half of the survivors may have neurologic or ocular sequelae. Fulminant infection with necrotizing vasculitis and disseminated intravascular coagulation may also be seen.[349]

Treatment. The best tactic is prevention. Pooled adult human globulin may be helpful. Adults have relatively high circulating antibody levels for both types 1 and 2 herpes simplex virus. The protective effect of such material is still in question, but judging the complexity of the host-parasite interactions mentioned above, and the safety of the procedure, we usually recommend the use of γ-globulin in documented perinatal and postnatal exposures.[283] Once the infant is born, and there is any evidence of herpes simplex infection, the clinician should act quickly. Baseline studies should be carried out to assess the degree of involvement. This includes examination of the CSF, liver function, and viral cultures of skin, throat, urine, CSF, and blood. Conjuctival swabs and any lesions should also be examined and cultured.

Systemic antiviral therapy is indicated when herpes simplex infection is diagnosed in the newborn. The currently available antiviral agents are most active when given early (within 3 days of onset) in infection and are, apparently, of low immediate toxicity. The long-term effects of such drug therapies are not yet apparent. Vidarabine is administered in a dosage of 15 mg/kg/day intravenously (over 12 h, at a concentration not exceeding 0.7 μg/ml of intravenous fluid) for approximately 10 days, or for 5 days after the newborn has been shown to be free of herpes virus.[467] A newer antiviral with more specific antiherpetic activity and low toxicity is acyclovir (Chapter 2). It is obvious from my comments that a team approach is useful in handling these rare but serious infections.

Prevention. Prevention of primary maternal herpes infections depends on education of the public about this venereal disease and avoidance of direct contact with suspicious lesions. Awareness of the natural course of recurrent genital herpes in women should foster logical approaches toward prevention of perinatal infection. Thus viral excretion is usually associated with the presence of external vulvar and vaginal lesions that persist for approximately 10–14 days.[6] Recurrent lesions are usually healed after 7–10 days, and the mean duration of virus excretion is 5 days.[180] Early and liberal use of antivirals (e.g., vidarabine, acyclovir) may shorten the course of viral excretion. This knowledge, coupled with virologic monitoring, should provide more exact guidelines for cesarean section and laboratory investigations. Cesarean section is indicated in mothers with virologically active lesions and intact (or ruptured less than 6 h) membranes, but vaginal delivery may be used if careful virologic surveillance indicates the maternal birth canal is free of virus.[58]

Herpes simplex viruses are spread by direct contact and are excreted in liberal quantities from skin lesions and, occasionally, from the upper respiratory tract. These viruses are extremely dangerous to newborn contacts.[149] It is essential, therefore, to isolate infants with suspected herpes simplex virus infections. The risk of newborn acquisition from infected mothers is about 50%, including infants born to mothers with virologically positive genital herpes infections and those with skin and/or breast lesions.[431] Handwashing is critical, and a private room is usually necessary. There is insufficient evidence to suggest that breast feeding creates a risk for transmission of herpes simplex virus to the infant,[240] unless breast lesions are present. The infected infant is also a threat to his caretakers. Those with skin breaks on their hands may develop direct inoculation lesions and carry virus to other infants as well.[5] The incidence of such spread is rare, but potentially disastrous.[192] While on the subject, nursery personnel with herpes labialis or herpes dermatitis should not be permitted to care for newborns while they have active lesions. Again, remember the mechanism of spread is direct, and some method of covering these lesions and preventing direct contact may be better than no protection at all.

Congenital Toxoplasmosis

Epidemiology. *Toxoplasma gondii,* a protozoan with a natural life cycle in cats, is an occasional pathogen in man.[142] It is most frequent in the Caribbean and least common in cold climates. Toxoplasma inhabit the cat's gastrointestinal tract and are excreted in cyst form in its feces. Ingestion of these cysts may cause human infection.[417,439] Primary infection in adults has also been associated with ingestion of viable cysts in undercooked meat,[235] raw goat milk,[376] and by leukocyte transfusion.[402] It is wise for pregnant individuals to avoid contact with cat litter and ingestion of undercooked meat. The ubiquitousness of this organism is suggested by serologic evidence of infection in 40–95% of females ages 25–35 years;[366] however, the expression of disease is limited.

Acquired Infection. Acquired toxoplasmosis is often asymptomatic but may manifest as lymphadenopathy with or without fever,[121] heterophile-negative infectious mononucleosis, or chorioretinitis.[181,252] Disseminated toxoplasmosis is potentially lethal in immunosuppressed patients, in whom combined infection with opportunists such as CMV can occur.[282] Reported manifestations of acquired toxoplasmosis also include myocarditis,[322] polymyositis,[378] hepatitis,[462] and brain abscess.[302] Primary infection is most dangerous to the developing fetus, whereas the danger of reactivation or chronic infection in the mother during pregnancy is poorly defined. Our understanding of the expression of toxoplasmosis in adults and the pathogenesis of congenital infection is far from complete!

Congenital Infection. Maternal seroconversion in the United States occurs in one or two of every 200 pregnancies, and approximately 45% of these infants will have congenital toxoplasmosis.[470] As with other congenital infections, the earlier in gestation the infection occurs, the more severe and generalized is the effect.[217,427] Thus, abortion may result from maternal infection around the time of conception, and multisystem involvement from infection acquired in the first and second trimesters. About 10% of these infants have chorioretinitis, 20% generalized disease, and 70% are asymptomatic.[416] Many of the latter may develop chorioretinitis later.[471] Generalized manifestations of intrauterine congenital infection may resemble those due to CMV, rubella, and herpes simplex infections. These include meningoencephalitis, often with intracranial calcifications, hepatosplenomegaly, and anemia.[416] CMV is the most frequently recognized cause of these problems; however, both diseases may cause psychomotor retardation. Other neurologic malformations noted in patients with congenital infection include anencephaly, microcephaly, anophthalmy, microphthalmy, and hydranencephaly.[37] A rare manifestation of congenital toxoplasmosis is bone (metaphyseal) involvement[308] and nephrotic syndrome,[390] reminiscent of that described in cases of congenital syphilis. In fact, it is possible that toxoplasmic chorioretinitis (an important cause of blindness) represents congenital acquisition and reactivation in most cases.

By the third trimester, acquired primary maternal toxoplasmosis will be transmitted to almost 65% of offspring; most of these infected infants will be asymptomatic initially.[416] A small percentage will develop jaundice, hepatosplenomegaly, and CSF pleocytosis in the first few months of life and some may develop chorioretinitis at any time.

Diagnosis. Diagnosis is usually based on serologic evidence[469] of infection in the infant or on culture of toxoplasma from the newborn's CSF or throat.[17] *T. gondii* has recently been isolated from amniotic fluid in two of three confirmed congenital cases.[428] The protozoan will replicate in epithelial cell tissue culture—handy because this is also used for CMV culture. Unfortunately, tissue culture is not yet very sensitive, and mouse inoculation (more sensitive) may require 4 weeks or longer to obtain results. If the infant's antibody titer is equal to or greater than the mother's, the diagnosis is supported. If the infant's antibody is predominantly of the IgM class or if IgG antibody persists at the same level or in increasing concentrations over the first few months of life, the diagnosis is confirmed.[463] Immunofluorescent IgM tests are technically exacting and may be falsely positive due to rheumatoid factor present in the serum of normals or in patients with autoimmune disorders;[478] a recently developed enzyme-linked immunoabsorbent assay (ELISA) method may avoid this pitfall.[330]

Treatment. Probably the most frustrating area of "toxoplasmology" concerns treatment. Although active in vitro, sulfonamides, pyrimethamine, spiramycin, and trimethoprim/sulfamethoxazole do little to arrest the results of infectious injury to the brain and the eye. The fact is that much of the injury has occurred by the time the diagnosis of congenital infection is made. French investigators report some success in prevention of congenital infection by using spiramycin during pregnancy.[117] This macrolide is not available in North America. Even if it were, the difficulty of diagnosing acquired toxoplasmosis makes the use of the drug problematic. One of the more obvious clues, chorioretinitis, usually represents local reactivation and may not reflect systemic spread. Faced with a pregnant patient with infectious mononucleosis due to toxoplasmosis, I would try spiramycin. On the other hand, maternal chorioretinitis during pregnancy, in the absence of systemic manifestations, would not be as urgent a problem for the fetus, particularly if supported by serologic evidence of past infection (low titer of IgG and no IgM toxoplasma antibody). What about the mother? There is little evidence that systemic antimicrobials dramatically influence the outcome of toxoplasma chorioretinitis, but specific drug therapy combined with corticosteroids is usually recommended as outlined below for congenital infections.

Newborns with congenital toxoplasmosis should be treated with oral sulfadiazine (50–100 mg/kg/day, divided b.i.d.) and pyrimethamine (1 mg/kg/day, given every third day) for 3 weeks to attempt to halt progressive infection.[366] Spiromycin is preferred in hyperbilirubinemic babies and in the first 2 weeks of life. This course is empirically repeated three times in the first year of life. In the face of active inflammation (i.e., chorioretinitis, jaundice, CSF abnormalities) add oral prednisone 2 mg/kg/day in two divided doses and taper after inflammation subsides. The risks of therapy seem outweighed in most cases by the gravity of the infection and its consequences. Remember, both antimicrobials interfere with folate metabolism, so use with care in malnourished or otherwise folate-deficient patients. It is useful to prescribe folinic acid, 5 mg twice weekly, during pyrimethamine therapy. Sulfadiazine and pyrimethamine can also induce hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, and sulfadiazine may displace bilirubin from albumin and cause crystalluria. So hydrate the patient and administer sulfadiazine after the first 2 weeks of life and then only in patients who are not hyperbilirubinemic (they may have toxoplasma hepatitis). In the final analysis, treatment is far from satisfactory for both acquired and congenital toxoplasmosis.

Prognosis. The prognosis of congenital toxoplasmosis is not fully appreciated. Although the majority of newborns who acquire *T. gondii* during intrauterine development appear normal at birth, their subsequent course may be graver than previously appreciated. Ophthalmologic, auditory, and neurodevelopmental deficits are common.[416] Parents can usually be reassured that subsequent pregnancies carry little risk of toxoplasmosis for their other offspring. As ususal in biology, exceptions have been reported.[424]

We have much to learn about the true frequency of congenital and acquired toxoplasmosis. This learning may be facilitated by new developments in culture and serologic diagnosis and by a better understanding of the epidemiology and host-parasite relationship in this condition. In the meantime, this infection poses an occasional, but extremely serious, threat to the developing fetus and newborn which may result in mental retardation, blindness, and neurodevelopmental abnormalities.

Hepatitis

Risk to the fetus and the newborn are outlined in Table 3-4. Acute hepatitis A in the mother during pregnancy may cause several problems including prematurity and neonatal infection.[425] Around the time of delivery the infant may become infected and manifest jaundice, although hepatitis A usually causes mild disease and has no carrier state. Hepatitis A antibody of the IgG class can also be found in newborn sera after

TABLE 3–4. Infectious Hepatitis in Newborns

	Type A	*Type B*	*Non-A Non-B*
Risks of maternal infection			
1st/2nd trimester:	Abortion	Low risk of abortion	Unknown
3rd trimester:	Prematurity Newborn infection if within 2 wks of birth	Prematurity Carrier: North American, low; Western Europe, low; Asia, high	Unknown
Prevention:	Immune serum globulin 0.5 ml IM	Hepatitis B immune globulin 0.5–1 ml IM at birth *plus* Hepatitis B vaccine at birth and 1 and 6 months later	Immune serum globulin 0.5 ml IM
Breast feeding:	No risk	Benefit outweighs risk in developing countries with high infant mortality due to gastrointestinal infection; risk outweighs benefit in developed countries.	Probably low risk

transplacental passage of maternal antibody: IgM antibody to hepatitis A usually indicates neonatal infection. Thus, if the infant and the mother have hepatitis A IgG antibody but no IgM antibody, active infection is unlikely.

Hepatitis B is more of a threat to the newborn because of the risks of severe acute disease[112] and long-term carriage; the latter may be associated with chronic active hepatitis and, rarely, hepatoma years later.[123,317] Certain hosts, such as Orientals, are more likely to become carriers when born to mothers with hepatitis B surface antigen in their blood.[159] Mothers with active disease and those with hepatitis B *e* antigenemia are most infectious to their offspring;[46] the presence of antibody to hepatitis B *e* antigen is not always protective.[407]

Little is known about non-A non-B hepatitis in newborns, although it is possible this infection may result from materno-fetal blood transfusion. Like CMV, infection is also associated with postnatal blood transfusions.

Prevention. Active and passive immunizations are recommended in cases where the infant is exposed to hepatitis B surface antigen.[90] Hepatitis immunoglobulin[47,223] together with hepatitis B vaccine,[40] may offer both early passive, and late active, protection.[432]

Isolation methods depend on knowledge of the type of hepatitis. Patients with type A infection usually excrete virus in their stools. Since fecal contamination involves the whole infant and his immediate environment, a single room, gown, handwashing, and careful disposal of excreta (double bagging and autoclaving) and linens (double bagging and high temperature laundering) are recommended. Isolettes cannot be relied upon for isolation as the exterior surface is inevitably contaminated.

Type B is spread predominantly by blood, although antigen has also been detected in saliva, breast milk, and other body secretions. Handwashing and avoiding direct contact with blood are of paramount importance and can be accomplished by precautions in handling blood and secretions. (Chapter 13). We favor avoiding breast feeding for HB_sAg-positive mothers in developed countries.[253]

Congenital and Neonatal Varicella

Expression of varicella infection in newborns is extremely variable,[114] ranging from mild rash in some to disseminated disease with a fatal outcome in others. This is true of both congenital and neonatal varicella. Varicella is predominantly an infection of young children and rarely complicates pregnancy. If it does, the frequency of serious consequences is unknown. The appearance of zoster during pregnancy is not considered dangerous, since humoral and cell-mediated immunity are usually intact in mother and neither transplacental nor neonatal infection should occur.

Transplacental immunity has been demonstrated in both full-term and pre-term infants, but may be low in those < 1000 g and < 25 weeks gestation.[459]

Clinical Manifestations. Manifestations of congenital varicella syndrome have included eye defects (chorioretinitis, microphthalmus, cataracts, and Horner's syndrome),[88] scar-like skin lesions and ulcerations,[61] hypoplastic limbs, CNS damage,[433] diaphragmatic hernia, and abdominal muscular defects. Although most of the defects have been noted after maternal varicella infection in the first two trimesters, skin ulcers have been reported in the infant of a mother with infection during the third trimester.[29] Herpes zoster may also be seen in children several months[125] to years after maternal intragestational varicella.[74]

Neonatal varicella is usually mild, but fatal infection with coagulopathy and widespread skin, visceral, and CNS involvement may occur.

Diagnosis. The diagnosis of varicella is usually evident from the typical skin lesions in the mother. Such lesions can provide material for presumptive diagnosis by examination of Tzank preparations or by electron microscopy, although neither test can differentiate herpes simplex from varicella virus. Demonstration of varicella antigen in vesicular fluid or culture of virus from the vesicle are diagnostic,[155] as is acquisition of humoral antibody by complement-fixation, fluorescent antibody membrane-associated antigen (FAMA),[160] or ELISA methods; the presence of IgM varicella antibody can be demonstrated by the ELISA technique in both the mother and the infant and indicates recent infection.

Treatment. Treatment of varicella infection during pregnancy is not usually attempted due to the potential teratogenicity of currently available antiviral therapies. Varicella zoster immune globulin or even pooled human immune serum globulin may be of benefit to the mother and her unborn child. Disseminated life-threatening illness in the mother or progressive infection acquired by the newborn should be treated with acyclovir. The exact dose of acyclovir is not established; however, 30 mg/kg/day for 7–10 days after clinical stabilization and beginning of resolution of the lesions is used. Some success has also been reported with the use of interferon,[24] although this approach remains experimental.

Prevention. Prevention of varicella is the key to obviating congenital defects and serious neonatal infection. Such prevention is usually naturally acquired after childhood infection. In infants younger than 25 weeks gestation and < 1000 g,[459] and in those mothers and/or infants who remain susceptible, varicella zoster immune globulin (VZIG) is indicated as early as possible after exposure to chicken pox or shingles.[356] One exception is the exposure of the infant to a mother with shingles. Since that represents a reactivation, the infant ordinarily should not be at risk. When in doubt, test the infant for varicella antibody, if possible. If not or if antibody is absent, give VZIG. The preventive dose of ZIG (0.1 ml/kg) or VZIG (Chapter 1) should be given to the mother during pregnancy and/or to the newborn exposed to mother who developed primary varicella within 5 days before delivery or during the neonatal period. Vaccination of susceptible adults before pregnancy is another approach, although the widespread application of vaccine may not be warranted considering the relative rarity of congenital varicella syndromes.

Thus, although varicella is rare during pregnancy and the peripartum period, the consequences for the fetus and newborn may be serious and longstanding. Simplified means for detecting and vaccinating susceptible females may provide the key to effective prophylaxis of these complications in the future.

Mumps

Intrauterine infection with mumps virus is infrequent and the consequences poorly understood. Isolation of mumps virus from amniotic fluid, placental, or fetal tissues[256] is diagnostic, but absence of a humoral immune response in the newborn does not rule out the possibility of congenital mumps infection. Apparently some infected newborns demonstrate only cell-mediated (e.g., mumps skin test) immunity after intrauterine experience with mumps virus.[1]

As with other congenital virus infections, first-trimester disease may be teratogenic, but the frequency of this consequence is unknown. Mumps has been associated with abortion or, occasionally, with microcephaly, hydrocephalus, or endocardial fibroelastosis.[135,426] Although cause and effect have not been established, placental and fetal lesions have been described in human intragestational mumps[157] after natural disease and after vaccination.[474] Congenital anomalies and/or low birth weight may result; however, many infants are normal.[319]

Perinatal mumps may develop when the mother has primary infection within a week of delivery; newborn illness is variable and pneumonia has been reported.[229] Generally mumps is a childhood infection and infrequent during pregnancy and the early newborn period. Newborn infants of immune mothers should be protected by transplacental immunity for at least 6 months.

Measles

Although measles is a preventable disease, parts of the world are still plagued by this infection. There is some controversy about nonspecific mechanisms operative in protecting young infants from measles, even if their mothers are susceptible.[163] The realities are that people of all ages are at risk of developing measles when in contact with carriers of the disease and should be protected.

Mothers who develop measles early in pregnancy may abort or give birth to a stillborn fetus. This may reflect congenital measles infection, although evidence for this is scanty, and it is more likely a nonspecific response to stress. When the mother develops measles around the time of delivery, the baby is expected to acquire measles within a 10–14-day incubation period. If the mother develops measles 2–3 weeks before delivery, the baby may have a very mild form of measles due to having acquired some of the newly developed maternal antibody. This "modified" measles is different than "atypical" measles that is seen after recipients of killed measles vaccine have been exposed to the wild virus. Modified measles is generally a mild form of measles. It is hoped that, with the more widespread application of live measles vaccination, this discussion will be of historic interest only.

Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus is present in rodents and rarely affects man. Acquired infection is most commonly associated with an aseptic meningitis syndrome, although other neurologic manifestations and parotitis have been reported. Approximately 20 cases of human intragestational infection have been described. The spectrum of newborn involvement has ranged from death due to meningoencephalitis early in the postnatal period, to chorioretinitis, hydrocephalus, and microcephaly in most of the survivors.[391] This condition can be suspected by a history of association with hamsters, mice, or guinea pigs. The virus can be grown in tissue culture but the diagnosis is most readily made by the complement-fixation or, more reliably, by the indirect fluorescent antibody method. There remains much to be learned about the frequency and the expression of congenital infection due to this virus. At the moment there is still no treatment. It seems wise for pregnant women to avoid contact with rodents.

Acquired Neonatal Infections: Specific Causes

Group B Streptococcus

Streptococcus agalactiae (group B) colonizes the maternal urethra, vaginal tract, and rectum, and the paternal urethra.[284] It is sexually transmitted but colonization is usually asymptomatic; occasionally there may be a vaginal discharge or fever. In the mother, group B Streptococcus can cause puerperal sepsis, endometritis,[466] and preterm delivery.[364] The biggest risk, however, is to the newborn. Anorectal[22] and/or vaginal colonization can be detected in up to 30% of pregnant females in the third trimester.[44] Approximately one-half to three-quarters of their offspring become colonized, and about 1–2% of these develop symptomatic infection.[31] The risk of infection appears enhanced in twins.[131]

Clinical Manifestations (Table 3–5). The most devastating form of infection is early-onset bacteremia with shock, pneumonia, and, occasionally, meningitis.[453] Maternal and perinatal complications, including prolonged rupture of membranes, are commonly present.[3] Group B streptococcal infection can masquerade as respiratory distress syndrome where the "hyaline membranes" are composed of sheets of streptococci,[233] or gram-negative septic shock.[143] A toxin with "endotoxin-like" properties has been detected in these bacteria[261] and enhancement of its vascular damage and shock effects by endotoxin has been demonstrated.[385] Localized newborn infections have also been described, including omphalitis, cellulitis,[32] impetigo-like skin lesions,[280] osteomyelitis,[216,301] and peritonitis.[84] A curious association of right diaphragmatic hernia with group B streptococcal pneumonia has also been reported.[189]

All three serotypes (I, II, III) can cause early-onset infection, although type III is most common in infections that are seen after the first week of age.[33] Type-specific opsonic antibody seems important in the expression of disease and attempts are in progress to develop methods for maternal immunization.[34,63,452]

Late-onset infection usually occurs in the second or third week of life and is less fulminant than early-onset disease. Hypotension is rare and meningitis common in these children. Bacteremia, arthritis, and osteomyelitis may occur. Although early-onset infection is clearly related to acquisition of the pathogen from the mother's vaginal tract (in utero acquisition has also been suggested),[30] late-onset infection may also be nosocomial (i.e., acquired from nursery mates and personnel).[38,64] It is also possible that prolonged colonization before invasion may protect the host from some of the devastating effects seen in early-onset infection.

TABLE 3–5. Early and Late Onset Group B Streptococcus Infections

	Early Onset	*Late Onset*
Age	< 5 days	> 7 days
Maternal factors	Obstetric complications	None
Predominant clinical feature	Septicemia, pneumonia	Meningitis
Serotype	I, II, III	III
Acquisition	Mother	Mother/nosocomial
Attack rates	1–4/1000 live births	0.5–1.5/1000 live births

Diagnosis. In addition to clinical features in the mother and the infant, early clues to the presence of group B Streptococcus include demonstration of gram-positive cocci in gastric or tracheal aspirate, or antigen or bacteria in serum, urine, or joint fluid. In culture, the organism may be more mucoid than other streptococci, and is occasionally nonhemolytic. Rapid methods for antigen detection include countercurrent immunoelectrophoresis, latex agglutination, and ELISA techniques.[219,354]

Treatment. Suspicion of the diagnosis should prompt appropriate management immediately (Table 3–6). In early-onset disease this includes aggressive diagnosis and management of shock as well as penicillin or ampicillin in combination with an aminoglycoside (gentamicin or tobramycin).[311] The aminoglycoside is necessary since gram-negative infection initially cannot reliably be differentiated from group B streptococcal disease, and may also be useful because of the enhanced rate of killing of some strains of group B Streptococcus by the combination in vitro[102] and in mice.[118] This approach may be necessary since some strains of group B Streptococcus are tolerant to the bactericidal effect of penicillin.[242] Recurrent infections with two such strains that were treated with penicillin or ampicillin alone were recently reported.[405]

Other approaches to therapy of early-onset infection include exchange and fresh blood transfusions,[104] leukocyte administration,[380] indomethacin,[395] and intravenous immunoglobulin.[145,381] Recurrences have been noted after group B streptococcal meningitis, prompting recommendations for high-dose (200,000–400,000 units/kg/day) penicillin therapy for a minimum of 2 weeks after sterilization of the CSF and clinical stabilization.[70] I also recommend the use of an aminoglycoside together with penicillin or ampicillin in CNS infections until bacteriologic steri-

TABLE 3–6. Antibiotic Treatment of Group B Streptococcus Infection

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Without Meningitis[a]
  Penicillin G IV 100,000 units/kg/day divided q 12 h in the first week of life then q 8 h; treat for 1 week after sterilization and improvement.
With Meningitis[a]
  Penicillin G IV 100,000 units/kg/day as above
    plus
  Gentamicin until bacteriologic cure:
    IM, IV, 5 mg/kg/stat, then 5 mg/kg/day divided q 12 h < 7 days of age, then 6–7.5 mg/kg/day divided q 8 h. Use 2.5 mg/kg q 18 h in neonates < 34 weeks. Monitor serum concentrations. After bacteriologic sterilization, penicillin G IV 200,000 units/kg/day divided q 6 h (provided renal function normal) for an additional 2 weeks.

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[a] If the infecting strain is tolerant to penicillin (e.g., MBC $\geq 8 \times$ MIC) add gentamicin for all infections and continue both drugs for the entire treatment course.

lization has been documented. The presence of ventriculitis, otitis media, subdural empyema, osteomyelitis of the skull, etc., should also be ruled out in cases demonstrating slow resolution and recurrences.[300]

Prevention. There is conflicting evidence about the use of antibiotics to prevent neonatal group B streptococcal infection. The most recent study of prophylactic penicillin in neonates, in fact, showed no decrease in the incidence of group B streptococcal infection.[360]

An alternative approach is to administer antibiotics to colonized mothers during labor.[62,482] In fact, methods are available to rapidly identify heavily colonized mothers directly from vaginal swabs.[228] However, the incidence of neonatal disease, in relation to maternal colonization, is generally too low to justify a prospective program to detect group B Streptococcus in the mother, in order to define the population at risk. Factors that increase the risk of neonatal infection and its severity may include heavy group B streptococcal colonization of the mother's vagina, premature onset of labor, and obstetric complications. In the presence of these risk factors, two approaches can be taken. One is to administer penicillin (500 mg potassium penicillin, four times a day) or erythromycin (500 mg erythromycin ethylsuccinate) during labor. These two oral regimens have been associated with markedly decreased maternal and infant colonization.[306] Alternatively, intravenous ampicillin (500 mg q 6 h) can be used.

Prognosis. Mortality rates of 50% are common in early-onset infection although these are lower (10–25%) in late-onset disease. The prognosis for survivors of meningitis is guarded, with 20–50% demonstrating severe neurologic sequelae.[214] The long-term outcome for survivors of bacteremia and other localized infections seems much better.

Other Streptococci

Although group A *Streptococcus pyogenes* was once a major cause of neonatal infection, it is infrequently encountered in nurseries today. Nonetheless, the potential for serious infections due to this and other groups of streptococci remains, and these bacteria should not be dismissed as contaminants when found in blood, CSF, urine, joint fluid, etc.[127] This is true for viridans streptococci as well, as illustrated by recently reported cases of neonatal sepsis and meningitis due to these bacteria.[71]

E. coli and Gram-Negative Enteric Infections

Next to group B Streptococcus, *Escherichia coli* is the most frequent cause of invasive bacterial infection of the newborn. The features and characteristics of *E. coli* infection can be used as a model for most gram-negative enteric bacilli causing neonatal infections. In some populations, *Staphylococcus aureus* is equally important. Remember the incidence of sepsis in developed countries is still only 3–5 per 1000 live births and of meningitis 1–2 per 1000 live births. Thus we are looking at relatively infrequent occurrences. However, in high-risk newborns, such as prematures and those with serious underlying conditions, the likelihood of *E. coli* infection increases. This is also true for populations where malnutrition, poor hygiene, and primitive living conditions exist.

Pathogenesis/Immunity. *E. coli* K1 is a particular serotype, characterized by a specific antiphagocytic polysaccharide capsular antigen, that causes approximately a third of the cases of sepsis and as much as 80% of meningitis due to gram-negative bacteria in newborns.[350] Most *E. coli* infections become bacteremic (even urinary tract infections) although entry and local inflammation may occur in the umbilical area or in the respiratory, gastrointestinal, or genitourinary tracts. Initial studies suggested that K1 antigen was responsible for virulence and that immunity to K1 might be protective for newborns. Recent investigations, however, indicate that other strains of *E. coli* transformed by cloned genes for the production of K1 capsular polysaccharide are not invasive.[406] Thus other components in addition to K1 capsular polysaccharide seem to be required to explain completely the virulence of these bacteria. Virulence factors of *E. coli* (and other gram-negative bacteria) are listed in Table 3–7 along with some clinical effects.

Clinical Manifestations. The clinical manifestations of *E. coli* K1 infections are not distinctive when compared with other gram-negative infections in the newborn. Sepsis and/or meningitis are usually of sudden onset; however, some cases of more insidious progression have been noted, with the diagnosis made as late as the second week of life. Surprisingly, endotoxic shock is less common in newborns than in older patients, but,

TABLE 3–7. *E. coli*: Virulence Factors

Bacterial Factor	*Effect*
Capsular antigens (e.g., K1)	Septicemia, meningitis
Endotoxin	Shock, disseminated intravascular coagulation
Hemolysins	Hemolysis
Enterotoxin	Diarrhea: watery
Heat-labile	
Heat-stable	
Enteroinvasion	Diarrhea: bloody
Pilus (surface colonization factor)	Diarrhea

when present, requires early diagnosis and aggressive management. Features are hypotension, bleeding, tachycardia, tachypnea, peripheral cyanosis, hypothermia, and poor muscular tone. In general, meningitis cases seem most virulent, although this may simply reflect late diagnosis.

E. coli plays a very limited role in acquired gastrointestinal infections in North American newborn nurseries, although this species continues to be an important cause of diarrhea with associated complications in developing countries. Part of effective control in those areas depends on the use of breast-feeding and improving hygienic practices.

The expression of *E. coli* infections, in addition to sepsis, meningitis, and gastroenteritis, is dictated by the organ involved. It is a common cause of urinary tract infection and an occasional cause of pneumonia in newborns. The toxicities of some of the products of these bacteria are exemplified by the reported observation of pneumatocele formation in *E. coli* pneumonia.[254]

Diagnosis. Diagnosis is made by gram smear and culture of appropriate material. Rapid identification of *E. coli* K1 can be made by agglutination of these bacteria by group B meningococcus antiserum, since these bacteria share capsular antigens. Hypotension and bleeding suggest the diagnosis, as does the presence of urinary tract abnormalities and/or infection.

Treatment. If hypotension is present, its treatment is of first priority. Thus, administration of fluids, dopamine, digitalis, as well as aggressive use of intravascular and urinary flow measurements, are critical. Initial antibiotic therapy of *E. coli* infections is dependent on the prevailing pattern of antimicrobial susceptibility in the nursery. These patterns change in closed populations in response to several factors, including the selective pressure of commonly used antibiotics.[115] β-Lactam and aminoglycoside antibiotics are usually used in combination in the initial treatment of neonatal septicemia and meningitis. Cefotaxime, or other newer cephalosporins, can also be used. In the case of *E. coli*, synergistic combinations are useful to treat multiply resistant organisms.[266] Commonly chosen are ampicillin plus gentamicin. Once susceptibilities are further characterized, single-drug therapy can be used in many situations, although synergistic combinations may be necessary for CNS infections or for those infections at sites where antibiotic concentrations may be low. Drainage of abscesses is important, as is correction of obstruction and other predisposing factors.

Prevention. Isolation is usually not necessary for infants with extragastrointestinal *E. coli* infections, unless they are harboring organisms that have bizarre antimicrobial susceptibility patterns that would be an extreme risk to other individuals in the unit. In such circumstances, enteric isolation in a private room is recommended. The ultimate goal of prevention of *E. coli* infections in newborns seems to have limited prospects at this point. It was originally thought that immunity against K1 antigen might offer protection; however, ignorance of other factors involved in virulence, and the low frequency of this infection in the total newborn population, are limitations of this approach. Yet, we are constantly reminded of the virulence of these and related bacteria and the importance of infection control techniques by periodic outbreaks of gram-negative bacterial infections in our nursery population.

Staphylococcus

Staphylococcus aureus colonizes many babies within the first 2 weeks of life without ill effects but may cause serious infections in some newborns. This is also true of *S. epidermidis*, which may be a cause of life-threatening septicemia[323] and which may be resistant to conventional antistaphylococcal drugs.[91] Bacteria are derived from direct contact with maternal flora, personnel, and environmental sources. The anterior nares, in adults, and the umbilical stump, in newborns, are the most frequently colonized sites.[204] Conditions that predispose to invasion include small size, repeated procedures that break the skin barrier,[263] and residence in high-risk nurseries, where understaffing and overcrowding play important roles.[186]

Staphylococci are extremely prevalent in both the animate and inanimate nursery environment. The potential for outbreaks is always there. This prompted the widespread use of hexachlorophene bathing for prevention of infection. Because of toxicity, that routine has largely been abandoned, with some resurgence of nosocomial epidemics.[238]

Clinical Manifestations. Staphylococci generally invade via the skin but rarely present in the first few days of life. Omphalitis, furunculosis, and abscesses are most common and may not develop until several days after birth or after discharge from hospital.[204]

Skin lesions may rapidly become bullous (Fig. 3–5) when due to specific strains of *S. aureus* that produce exfoliation.[141] This is a potentially fatal lesion in a newborn and must be managed with systemic antistaphylococcal drugs. The most severe example of progressive staphylococcal skin infection is manifest by confluent bullae and desquamation with profuse bacterial growth in skin lesions and in the blood. Even the toxic-shock syndrome may occur in newborns.[173] Pneumonia and bone and joint infections are not uncommon, and can be very difficult to diagnose. Meningitis is rare and usually seen only in patients with meningomyelocele or other malformations communicating with the CNS. Surgery, such as ventriculo-peritoneal shunt implantations, is also a major predisposing factor for meningitis. Endocarditis may occur in infants with

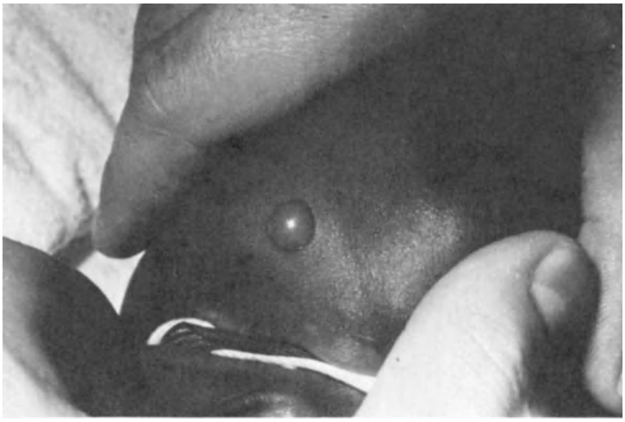

Figure 3-5. Bullous lesion due to *Staphylococcus aureus.*

or without cardiac anomalies. Staphylococcal enterocolitis[183] and necrotizing fasciitis[461] are rare but serious examples of newborn staphylococcal infections.

Diagnosis. Abscesses should be gram-stained, as should pustules, joint fluid, and blood buffy coat in certain situations (methylene blue or giemsa is better for the latter). Visualization of gram-positive cocci in these smears or in CSF, urine, or other fluid should suggest Staphylococcus until proven otherwise; group B Streptococcus, however, is more common. Confirmation by standard bacteriologic methods should then be made.

Staphylococcus epidermidis can also be an important newborn pathogen and should not be discounted as a contaminant in cultures of blood, CSF, urine, or joint fluid. Because of this, a skin culture (premoistened swab) of the prepared (75% alcohol followed by povidone-iodine) site should be obtained before blood culture, lumbar puncture, arthrocentesis, etc., in situations where staphylococci are suspected (e.g., previous positive culture, skin lesions, Staphylococcus outbreak, etc.).

Treatment. Systemic antibiotic therapy (e.g., dicloxacillin 25–50 mg/kg/day in four divided doses) is recommended for the treatment of staphylococcal infections in infants older than 1 week of age (25–50 mg/kg/day divided q 8–12 h is used in the first week of life). Daily bathing with 3% hexachlorophene and, occasionally, incision and drainage are used to hasten resolution of localized infection and to prevent invasive infection. Prematures should not receive more than three baths and hexachlorophene should be rinsed off thoroughly in all infants. Hexachlorophene should not be used in infants with extensive skin lesions because of the danger of significant systemic absorption of drug.

Systemic invasion by Staphylococcus may result in bacteremia, osteomyelitis, arthritis, endocarditis, and other visceral abscesses; these may also occur with skin lesions. Antibiotic susceptibility patterns of prevalent staphylococcal strains are useful for selection of initial therapy. This is particularly important in view of increasing reports of methicillin, gentamicin, and multiple antibiotic-resistant staphylococci in newborn units.[445] Use of topical antimicrobials, such as gentamicin, frequently selects for resistant staphylococci in nursery units.[172]

Prevention (Table 3–8). Staphylococcal skin infections represent a considerable nosocomial infection problem. Because of its toxicity,[294] routine hexachlorophene washes of all infants are now reserved for use during nursery outbreaks.[447] Currently, application of bacitracin[75] or triple dye[76] to the umbilical stump shortly after birth is effective in retarding staphylococcal colonization, although studies of toxic and microbiologic consequences of these procedures are incomplete. Moreover, triple dye may not effectively reduce group B Streptococcus and *E. coli* colonization.[35] Colonization rates correlate poorly with infection rates although a marked increase in prevalence of specific strains of Staphylococcus may be associated with nosocomial infections. This requires further study. Control of infections requires ongoing attention to isolation techniques (handwashing is critical!), avoiding the use of topical antibiotics that select for resistant bacteria, and prompt therapy of specific infections. Cohorting

TABLE 3–8. Plan for Control of Staphylococcal Colonization and Infection in Newborns

At Birth
  Apply bacitracin to umbilicus.
  Rinse with clean warm water.
During Outbreaks
  Wash babies q.d. with 1% hexachlorophene solution and wash off, for duration of outbreak (limit to three in prematures).
  Review and enforce isolation and infection control procedures.
  Use hexachlorophene or chlorhexidine for handwashing during outbreaks.
Persistent Spread in Nursery
  Cohort patients to three separate areas with separate staff:
  1. Patients with staphylococcal infection or colonization with outbreak strain.
  2. Patients present during outbreak.
  3. New admissions after initiation of cohort.
Persistent or Multiple Staphylococcal Nursery Epidemic
  Type infecting and colonizing staphylococcal strains.
  Identify and treat carriers.
  Consider excluding carriers from nursery.
  Consider bacterial interference.

of patients and staff may be needed in some cases. Gram-negative nosocomial infections, due to sensitive or resistant strains, illustrate similar principles. Many other approaches are possible, but each needs to be examined for possible adverse effects. For example, perinatal exposure to povidone-iodine may cause transient hypothyroidism in the newborn.[258]

Occasionally, persistent and recurrent nursery epidemics require specific characterization of the responsible strain(s) by phage-typing and subsequent identification of carriers. Aggressive systemic and topical antibiotic therapy (e.g., rifampin plus cloxacillin systemically + bacitracin topically) have been successful.[465] If the effect on carriage is only transient, implantation of a strain of *Staphylococcus epidermidis* (e.g., strain 502A) in the anterior nares of carriers may prevent recolonization with more virulent staphylococci (bacterial interference).[422] Aggressive antibiotic treatment and use of bacterial interference are rarely needed when infection control techniques are carefully followed and isolation procedures enacted early in the course of nosocomial spread.

Salmonella

Manifestations. The newborn is special with regard to contact and infection with Salmonella for several reasons. First, he may be heavily exposed to the organism by contact with maternal gastrointestinal and genital flora before and during delivery. Nosocomial nursery outbreaks have also been reported.[295] Furthermore, Salmonella presents in a nonspecific fashion in newborns, occasionally without diarrhea. Even with diarrhea, the incidence of extragastrointestinal complications is increased during the first 3 months of life, and particularly in the newborn, where rates as high as 5% have been described.[111] Exact reasons are unclear, although immunologic and gastrointestinal immaturity, neutral pH of the stomach, and relatively sluggish local defenses (motility, mucus) seem important. Involvement of the meninges and almost every organ and tissue of the body has been reported.[464] Salmonella meningitis, pneumonia, and bone and joint infections are particularly difficult to diagnose and treat. Malnourished infants are also at increased risk for extragastrointestinal invasion by Salmonella.

Treatment. For these reasons, a complete septic workup should be performed in newborns with suspected Salmonella infection or colonization, which should include examination of the CSF. Thereafter, therapy should be initiated in symptomatic patients, based on in vitro susceptibility studies or at least epidemiologic data. This is true even if the disease is apparently localized to the gastrointestinal tract. Ampicillin, cefotaxime, chloramphenicol, or trimethoprim-sulfamethoxazole are all useful, but sensitivities vary and the latter treatments are relatively contraindicated in young infants. Severe and prolonged cases of Salmonella enterocolitis may improve with a combination of oral (neomycin, kanamycin, or gentamicin) and parenteral antibiotics. Therapy can be stopped in newborns with disease confined to the gastrointestinal tract after cessation of gastrointestinal symptoms; in those with extragastrointestinal complications therapy should be prolonged for at least a week after documentation of sterilization of the infected site. In the case of meningitis, the total duration of therapy should be at least 3 weeks, because of clinical experience with relapses in this condition. Followup is essential considering the fact that prolonged fecal Salmonella excretion (8–12 weeks in 25% of infants under 3 months of age)[234] is common in young infants and relapses (particularly with meningitis) and other late complications can occur.

Listeria

Intrauterine *Listeria monocytogenes* infection may result in abortion early in gestation and stillbirth later on,[262] or congenital infection with early neonatal death.[251] These events usually parallel systemic maternal infection, clinically evident by fever and nonspecific signs of bacterial infection. A history of repeated abortions may suggest chronic genital Listeria infection in some cases. Although animals may be infected with the same strains, few patients have suggestive occupational histories. Laboratory-acquired, nosocomial, and soil-acquired infections are known.

Clinical Manifestations. Newborns acquiring Listeria late in pregnancy or during birth manifest diverse clinical signs ranging from septicemia to focal skin lesions. Two clinical syndromes, reminiscent of group B streptococcal infections, are seen.[129] The first (early onset) presents in the first 2 days of life and is characterized by septicemia and high mortality rates. Obstetric complications, malaise and, occasionally, vaginal discharge or diarrhea are noted in the mother, and prematurity, bacteremia, pneumonia, and focal granulomatous abscesses are seen in the infant. As with group B streptococcal infection, many newborns with the early form[365] present with respiratory distress and severe pneumonia.

The second form (late onset) presents after the fifth day of life and represents infection acquired during delivery or postnatally. Meningitis is the predominant feature and the course of illness is less fulminant, although recurrent infection and hydrocephalus may occur. Meningitis may be associated with mononuclear CSF pleocytosis.

Diagnosis. The diagnosis of listeriosis is suggested by the clinical picture and gram stain visualization of pleomorphic gram-positive bacteria—so pleomorphic, in fact, that both cocci and rods may be present in the same smear. Isolates can be examined quickly for characteristic "tumbling" motility present at 4°C. Colonies on blood agar may produce β-hemolysis and resemble group A streptococci. Unlike the latter, however, they produce peroxidase and are bacilli on gram stain. Although reasonable growth rates are seen in blood and CSF, cultures from other sites may grow more slowly and should be kept for 3 weeks, if this diagnosis is suspected.

Treatment. Treatment of listeriosis is most often initiated with a combination of ampicillin and an aminoglycoside, such as kanamycin or gentamicin. This combination offers an advantage over ampicillin alone, probably because the two drugs accelerate the rate of killing of Listeria and are synergistic in vitro for some strains.[384] Two weeks of therapy with both drugs is usually required. The outcome is favorable in most cases, the exception being the infant presenting at birth or in the first day of life with fulminant sepsis and meningitis, often complicated by disseminated intravascular coagulation and bleeding.

Isolation. Since nursery cross-infection and spread from an infected mother have been reported,[231] enteric isolation is indicated until bacteriologic cure has been documented.

Syphilis

It is unclear why acquired and congenital forms of syphilis are not occurring more frequently while the incidence of gonorrhea and other sexually transmitted diseases seem to be increasing at an alarming rate. This situation may change, however, since a 30% increase was noted in reported cases of acquired syphilis in adults in the United States in 1980. Considering the serious consequences and the fact that reinfection in the mother is possible, serologic screening of pregnant females seems warranted. If negative, the test should be repeated in the third trimester or at the time of delivery.[14] Appropriate treatment of the mother is effective treatment for the infant. Prevention of tissue invasion and destruction in the fetus and newborn is critical.

Pathogenesis. Spirochetemia in the mother rarely results in marked placentitis or fetal infection in the first 4 months of pregnancy. Abortion, however, can result. Similarly, stillbirth and prematurity may result from maternal infection later in pregnancy. Treponema organisms invade virtually all tissues of the infant; hence clinical manifestations are diverse.

Clinical Manifestations. Uncommon, but often not easily diagnosed, congenital syphilis has many unusual features, some of which are listed in Table 3-9. Most affected infants appear normal at birth, although they may be premature and small. A few also have hydrops fetalis, hepatosplenomegaly and jaundice, lymphadenopathy, and nasal discharge.[28] This white or blood-tinged discharge and any mucous membrane or skin

TABLE 3-9. Features of Congenital Syphilis

- Early
  - (< 2 years of age)
  - Small for gestational age
  - Prematurity
  - Hemolytic anemia, thrombocytopenia
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Placental villitis and perivasculitis
  - Rash
    - Maculopapular
    - Vesiculobullous
    - Condyloma lata: perioral, perianal
  - Jaundice
  - Nasal discharge
  - Periostitis: pseudoparalysis
  - Meningitis
  - Nephrosis
  - Eye: chorioretinitis, glaucoma, uveitis
- Late
  - (> 2 years of age)
  - Interstitial keratitis
  - Nerve deafness
  - Dental abnormalities
  - Facial bone abnormalities
  - Palatal perforation
  - Sabre shins
  - Skin lesions: rhagades (linear scars) around mouth, nostrils, anus
  - Nephrotic syndrome[367]
  - Synovitis

lesion (usually maculopapules, but these can ulcerate), which generally are present on the buttocks, back, thighs, and soles, are laden with high concentrations of infectious organisms—beware!

Some congenital findings, such as anemia, periostitis, jaundice, or hepatitis, may not become evident for several months.[177] Other changes, reflecting tissue damage and growth become obvious only after 1 or 2 years.

Diagnosis. The first clue to the diagnosis may be clinical signs in the mother or the infant, a history of venereal disease, or a positive serologic screening test in the mother, the most specific being the fluorescent treponemal antibody-absorbed (FTA-ABS). Placental inflammatory lesions may also suggest the diagnosis.[375] A positive Venereal Disease Research Laboratory (VDRL) or FTA-ABS in the newborn's blood may reflect passively transferred maternal antibody. On the other hand, FTA-ABS antibody of the IgM class suggests intrauterine fetal infection, particularly in the absence of rheumatoid factor and placental abnormalities leading to materno-fetal transfusion.[370] Positive serologic results in the face of a history of inadequate therapy or possible reinfection, or in the presence of clinical, radiographic, or microbiologic evidence, should be considered an indication for therapy. Microbiologic evidence usually means dark-field evidence of spirochetes in material from membrane or skin lesions or discharge. When doubt exists and more than 3 days are required for serologic confirmation (quantitative VDRL in the infant equal to or greater than the mother's, IgM FTA-ABS, serial VDRL examinations), it is usually advisable to treat.

Treatment. Benzathine penicillin G 2.4 million units IM remains the treatment of choice for adults with syphilis. Cephalosporins can be used in penicillin-allergic subjects. Both regimens effectively treat the fetus as well. Erythromycin, sometimes used for treatment in penicillin-allergic patients, may not cross the placenta reliably, and thus newborns may still be infected even though the mother has been treated. Penicillin treatment is recommended for these newborns.[73] Asymptomatic infants without signs of syphilis (including normal CSF) should receive benzathine penicillin G 50,000 units/kg IM. The recommended approach for treating symptomatic newborns is to assume the presence of neurosyphilis and treat with aqueous penicillin G 50,000 units/kg IV or IM × 10 days.[299] This does not obviate the need for CSF examination for pleocytosis and VDRL, which are used for followup and prognosis. Lesions should become noninfectious after 48 h of appropriate therapy.

Prognosis. As in the mother, serologic tests for syphilis may remain positive in more than half of adequately treated patients. These titers will slowly fall (over 6 to 12 months) and should be followed, as should any CSF change. Infants who are symptomatic at birth are likely to develop eye and teeth changes; if neurosyphilis is present, this may also be partly irreversible. The more severe the intrauterine infection and the longer the interval between acquisition of infection and treatment, the more likely late congenital manifestations will occur.

Gonococcal Infection

Manifestations. Urogenital infections due to gonorrhea are common in pregnancy, especially in certain populations. This sexually transmitted infection has several consequences to the fetus and the newborn. Initially, maternal gonococcal infection, even if asymptomatic, may be associated with abortion, prematurity, low birth weight, and premature rupture of the membranes.[195] Fetal gonorrhea has also been described.[336] If the mother is infected at the time of delivery, neonatal gonococcal infection may be limited to the eye (rarely skin,[369] mouth, vagina)[421] or become generalized. In the latter instance, sepsis, arthritis, pneumonitis, and, occasionally, meningitis can be seen.[247]

Eye Infection. The commonest expression of infection with *Neisseria gonorrhoeae* in the newborn is gonococcal ophthalmia neonatorum, a frequent cause of blindness in the preantibiotic era.[440] Neonatal eye infection due to gonorrhea may be apparent at birth; however, more typically, it becomes obvious between 2 and 5 days after delivery. There is usually a profuse purulent discharge and associated conjunctivitis.

Diagnosis. Examination of the purulent exudate shows polymorphonuclear leukocytes, many containing gram-negative cocci in pairs. Diagnosis is confirmed by culture. Maternal vaginal, cervical, anal, and pharyngeal cultures should be placed on Thayer-Martin media, a selective agar intended to inhibit the growth of pathogens other than the gonococcus.[103] This medium is also appropriate for cultures of the infant's eyes, skin, and external ear and gastric aspirates. Chocolate agar is appropriate for isolating *Neisseria gonorrhoeae* from CSF, urine, and other normally sterile body sites. Commercial blood cultures should support growth of this organism as well. However, conditions that markedly inhibit growth of other Neisseria species, i.e., dry and cold, also inhibit growth of *Neisseria gonorrhoeae.*

Treatment (Table 3-10). If the infant shows signs of gonococcal infection of the eye, systemic therapy with penicillin is indicated. This should also be done if the mother is discovered to have gonococcal colonization with or without symptoms. In such an instance, 20–50,000 units/kg of a single dose of aqueous crystalline penicillin G administered shortly after birth should suffice, with prematures receiving the lower dose. This single dose of penicillin is effective prophylaxis against ophthalmia neonatorum. Newborns with other gonococcal infections should receive 75–100,000 units/kg/day intravenously in two to three divided doses for at least a week for septicemia and arthritis, and at least 10 days for gonococcal meningitis. Alternate therapy, such as cefoxitin, may be necessary in infections due to penicillin and/or spectinomycin resistant strains.[83]

Prevention. Treatment of symptomatic or asymptomatic gonorrhea in the mother is the best method of prevention of neonatal infection. With or without such treatment, ophthalmic prophylaxis is recommended for all newborns.[97] This should be in the form of 1% silver nitrate solution in single-dose ampules or sterile ophthalmic ointment or drops of tetracycline (1%) or erythromycin (0.5%) in single-use containers.[81] However, tetracycline is not very effective in preventing chlamydial conjunctivitis.[368]

TABLE 3-10. Treatment of Neonatal Gonorrhea

Condition		*Drug*	*Dose (units/kg/day)*	*Frequency (duration)*	*Route*
Maternal gonorrhea	Premature	Aqueous penicillin G	20,000	1 dose	IM or IV
	Full-term	Aqueous penicillin G	50,000	1 dose	IM or IV
Treatment for:					
Ophthalmia		Aqueous penicillin G	50,000	q 12 h first week q 8 h after first week (7 days)	IV
Systemic (disseminated)		Aqueous penicillin G	100,000	q 12 h first week, q 8 h after first week (7 days)	IV
Meningitis		Aqueous penicillin G	100,000	q 12 h first week, q 8 h after first week (10 days)	IV
Penicillin-resistant gonorrhea		Cefoxitin	100 mg/kg/day	q 8 h	IV

Although flushing of the eyes after instillation of silver nitrate is often recommended, there are little data to show that this effectively reduces the incidence of chemical conjunctivitis. If flushing is performed, at least 15 sec should elapse after instillation of the silver nitrate before saline washing. Many physicians also recommend delaying prophylaxis for 1 h in order to establish maternal-infant eye contact and bonding.

Consideration of other sexually transmitted diseases should also be made in each of these cases. When gonococcus is found, a search for *Chlamydia trachomatis,* syphilis, herpes simplex, and CMV should probably also be included. Erythromycin prophylaxis and/or therapy may be most appropriate when combined infection and/or colonization with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are detected in mother. With early diagnosis and effective treatment, gonococcal infection in newborns should resolve rapidly without sequelae.

Tuberculosis

Tuberculosis continues to be a worldwide problem. A resurgence of tuberculosis in urban populations in North America has been noted recently, due to both endemic disease and importations.[220] Travel and immigration patterns are such these days that constant vigilance is necessary in order to avoid missing this important diagnosis.

Maternal Infection. During pregnancy, tuberculosis presents a considerable risk to the mother as well as the infant.[168] It is suggested that immune and hormonal changes enhance the mother's susceptibility to reactivation tuberculosis, but the severity of infection does not seem to be increased. Primary or reactivation tuberculosis may occur in both pulmonary and genital sites and miliary spread is possible. Routes of transmission to the fetus and newborn are: intrauterine (which occurs after maternal endometritis, placentitis, and hematogenous spread to the fetus); during delivery, particularly if genital tuberculosis is present in the mother; and after delivery, by airborne or direct transmission from the mother or other contacts with active pulmonary tuberculosis.

Congenital/Peripartum Infection. When intrauterine infection occurs early in pregnancy, abortion results. Serious in utero infection later in pregnancy may also be associated with stillbirth or severe congenital infection.[327] Third-trimester and peripartum-acquired tuberculosis may manifest diverse signs in the newborn. Most commonly, the infant is asymptomatic at birth, although signs may be present if significant placental and uterine infection has occurred shortly before delivery. These infants may have pneumonia and significant liver involvement[184] as well as failure to thrive, jaundice, hepatomegaly, and meningitis. Usually, however, these signs develop only after the newborn begins to acquire delayed hypersensitivity to *Mycobacterium tuberculosis.* Pallor, lymphadenopathy, and papular or pustular skin lesions may also be seen.[184] The interval between exposure and the onset of signs in newborns is variable but can be as long as 5 months.[423]

Diagnosis. The diagnosis of tuberculosis must be made early if effective therapy is to be prescribed for both the mother and the infant. Suspicion of the diagnosis depends on history and recognition of populations with endemic tuberculosis. In North America this includes Eskimo and Indian populations and recent immigrants from Southeast Asia, South America, and other endemic areas.

Diagnosis may be suggested by the presence of pulmonary or genital disease in the mother before or during pregnancy. Appropriate skin tests, cultures, and radiographs of the mother and contacts are indicated. Pregnancy does not depress skin test reactions. Adequate shielding of the mother's abdomen and pelvis should protect the unborn fetus from the untoward effects of radiation, even in the first trimester of pregnancy. Tuberculosis may also be suspected at the time of delivery by noting focal lesions on the placenta. In such a situation the placenta should be examined histopathologically for the presence of granulomas. This material and amniotic fluid should also be stained and cultured for acid-fast bacilli.

The infant should be examined and tracheal and gastric aspirates, as well as CSF and urine, should be stained and cultured for acid-fast bacilli. If hepatomegaly is present, liver biopsy should be considered. The liver is one of the best tissues for recovery of *M. tuberculosis* in the newborn and infant.[184] Cultures of skin lesions, if present, are also useful. The infant's skin test is usually negative at birth and requires from 4 to 12 weeks for conversion after intrauterine or perinatal exposure.

Management. If the mother has asymptomatic skin test conversion during or before pregnancy, she should receive prophylactic isoniazid 300 mg (5 mg/kg) given once daily for 1 year. Prophylaxis of the mother during pregnancy is controversial because of the possibility of adverse effects, albeit uncommon, in the fetus. Physicians caring for pregnant patients with positive skin tests without isoniazid should exercise extremely careful observation for signs of active disease, since this carries considerable risks for the unborn child. I favor the use of prophylaxis if skin test conversion occurs during pregnancy. If the patient's skin test status is unclear before pregnancy and she is otherwise healthy, observation without drug may be preferable.

If the mother has active disease, at any time, appropriate treatment is essential, despite the theoretical risks of teratogenicity and other fetal injury by currently used antituberculous medications. Isoniazid and ethambutol are preferred, although rifampin may be added in selected cases.[408] The risk of fetal deafness is high with streptomycin. Therapy of drug-resistant cases requires the use of additional drugs (pyrazinamide, ethionamide, cycloserine, capreomycin, or viomycin), with greater risks of toxicity and teratogenicity.[168]

Adequate treatment of the mother and other infected household contacts should exclude the possibility of neonatal tuberculosis in most cases. Should therapy not have been initiated before delivery, then several considerations are necessary for the newborn. Those who are symptomatic at birth should be treated in the classic fashion. At least two drugs are required. These are isoniazid 10 mg/kg/day (orally once daily; IM divided twice daily) and rifampin, 15–20 mg/kg/day (once daily). A recent report suggests that the more toxic streptomycin can be omitted.[184] Although ethambutol has been used, experience in newborns is limited. Of particular concern is the developing optic nerve, which may be unusually susceptible to the toxic effects of ethambutol.

More commonly, the newborn is asymptomatic and tuberculosis is diagnosed in the mother around the time of delivery or shortly thereafter. In such a circumstance several programs have been suggested (Fig. 3–6). One recommends separation of the infant and the mother until the active disease is under adequate treatment and the mother is noninfectious. This usually requires appropriate antituberculous therapy for at least 2–6 weeks; however, patients with extensive cavitary disease may be infectious for longer periods.[334] During this period of separation the newborn can be treated with isoniazid after a complete diagnostic evaluation for the presence of tuberculosis. Skin testing of infants should be done shortly after delivery, although it would be extraordinary to find delayed hypersensitivity present at that time. This skin testing should be repeated at monthly intervals. If the skin test is negative by 3 months of age, isoniazid can be discontinued. Then a decision can be made about bacillus Calmette-Guerin (BCG) prophylaxis. If the only contact was the mother, who is now effectively treated, isoniazid prophylaxis, periodic testing, and careful clinical surveillance of the newborn are adequate. If, on the other hand, other exposures are possible due to complicated disease in the mother, poor compliance, or social and ethnic factors that predict frequent tuberculosis contact for the infant, BCG should be administered.[237] This should be followed by a tuberculin skin test 6 weeks later. If the skin test is negative, BCG immunization should be repeated. Quantitation of this skin test reactivity provides a guideline for assessment of future diagnostic tuberculin skin testing. In selected situations (e.g., difficult to avoid exposure of newborn to tuberculosis, poor compliance) BCG and isoniazid may be administered simultaneously.[353]

Nosocomial spread of tuberculosis is also possible.[423] The risk of spread in nurseries is reduced by use of ultraviolet light, efficient ventilation, and adequate space.[79] When an active case of tuberculosis is identified in a nursery, extensive skin testing, clinical surveillance, and selected

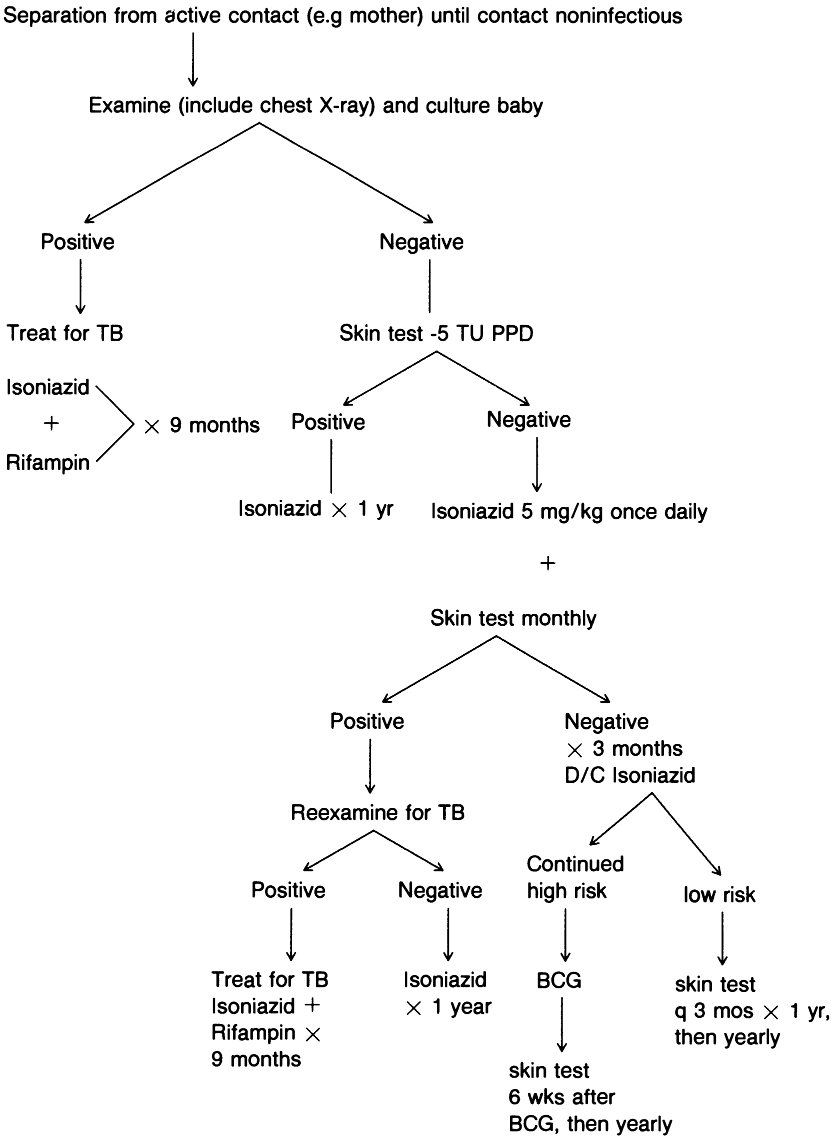
Separation from active contact (e.g mother) until contact noninfectious
Examine (include chest X-ray) and culture baby
Positive
Negative
Treat for TB
Skin test -5 TU PPD
Isoniazid + Rifampin × 9 months
Positive
Negative
Isoniazid × 1 yr
Isoniazid 5 mg/kg once daily
+
Skin test monthly
Positive
Negative × 3 months D/C Isoniazid
Reexamine for TB
Positive
Negative
Continued high risk
low risk
Treat for TB Isoniazid + Rifampin × 9 months
Isoniazid × 1 year
BCG
skin test q 3 mos × 1 yr, then yearly
skin test 6 wks after BCG, then yearly

Figure 3–6. Management of newborns exposed to tuberculosis.

radiographic studies are required. Isoniazid prophylaxis should be prescribed for 3 months for newborns during the skin test and clinical surveillance period.[275] Consideration for prophylaxis and repeated skin testing should also be given other intimate contacts. Children under the age of 6 years are particularly at high risk for the development of tuberculus meningitis and miliary spread.[202] Since this may be of sudden onset and fulminant, prophylactic isoniazid is usually indicated for infants and children exposed to active disease. If their skin tests are negative after 3 months, prophylaxis can be discontinued.

Anaerobes

Anaerobic infections may occasionally include life-threatening bacteremias, or, rarely, meningitis. An example is *Bacteroides fragilis* meningitis, which is often followed by hydrocephalus and brain injury.[265] The newborn is a highly susceptible host! An anaerobic wound infection today may be bacteremia and meningitis tomorrow. Here again, topical antibiotics or local care alone should be used with extreme caution when dealing with omphalitis and a variety of wound and skin infections in newborns.

Fungal Infections

Intrauterine Candidiasis. The most frequently encountered fungus in the neonatal period is *Candida albicans.* Approximately 1–3% of normal newborns acquire sufficient concentrations of Candida to manifest oral thrush, often associated with Candida diaper dermatitis. A much smaller percentage of newborns are infected in utero, probably secondary to ascending infection from the mother's heavily colonized vagina.[225] The placenta and cord of such infants may have abscesses appearing as white raised plaques on their surfaces; these infants may be born with oral and cutaneous candidiasis.[113] The appearance of extensive skin lesions at the time of birth should suggest this diagnosis, although the differential diagnosis should include congenital syphilis, staphylococcal infection, group B streptococcal infection, *Listeria monocytogenes,* herpes simplex, varicella, and erythema toxicum.

Postnatal Candidiasis: Skin and Mucous Membrane Involvement. About 10% of newborns acquire the yeast after passage through the asymptomatically colonized maternal genital tract and Candida takes up residence on the respiratory and gastrointestinal mucous membranes without any clinical manifestations.[288] For example, 55% of 56 infants became colonized by their third day of residence in a neonatal intensive care nursery.[288] When these infants are born with, or develop, predisposing conditions, Candida colonization increases and the yeast may become invasive. Small infants, those with immunologic abnormalities (including malnutrition), those receiving antibiotics or intravenous alimentation, and those with extensive surgical procedures are at highest risk of invasive candidiasis.[296] Treatment with antibiotics in the absence of other underlying conditions usually predisposes to oral thrush, characterized by white plaques diffusely located throughout the oral cavity. Examination of wet or gram-stained smears prepared from any of these lesions will reveal budding yeasts and occasional hyphae. Cultures will confirm the diagnosis. Treatment consists of discontinuing the antibiotics, if possible, and application of topical nystatin 50,000 units/ml (1 ml six times daily). Other topical agents, such as clotrimazole, can also be used.

Postnatal Candidiasis: Invasive. It is useful to administer oral nystatin when prescribing antibiotics for an infant with multiple predisposing conditions. When, despite this prophylaxis, the infant develops mucous membrane and/or skin lesions, the clinician should be wary of systemic candidiasis. Occasionally, candidemia and candiduria are transient when associated with indwelling intravascular and urinary catheters, respectively. When Candida is isolated from these sites, the catheters should be removed and cultures repeated thereafter. Persistence of Candida in the blood or urine must be taken as evidence of systemic infection. Repeated cultures should be obtained and the infant examined for the presence of endophthalmitis, endocarditis, nephritis, meningitis, pneumonitis, and arthritis. Abdominal masses may indicate focal Candida abscesses as well.[224]

Antifungal Therapy. Having performed the above examinations, it is wise to begin amphotericin B therapy. Newborns tolerate amphotericin well, hence a loading dose of 0.1–0.2 mg/kg can be used and increased daily to 0.5 mg/kg/day. Adequacy of amphotericin concentrations in body fluids should be measured by inhibitory and killing titers.

When systemic candidasis includes meningitis, flucytosine (5-fluorocytosine) should be added in a dose of 100–200 mg/kg/day administered orally or intravenously.[89] It is given every 12 h in the first week of life, every 8 h in the second week, and every 6 h thereafter. This combination may be synergistic and often facilitates a reduction in the total amount of each drug required, thereby minimizing their toxicities. In addition, some drugs, such as amphotericin and miconazole, diffuse poorly into CSF and may be inadequate as single drug treatment of meningitis.

Since it is well concentrated in urine, flucytosine can be used alone for selected genitourinary candidiasis. Newer agents, such as miconazole, ketoconazole, and rifampin may also be useful for selected infections.[132] Optimal antifungal therapy can be partly predicted by in vitro susceptibility tests. Furthermore, laboratory studies to rule out antagonism of combinations and to monitor fungicidal activity as close to the site of infection as possible are mandatory in these rare but complicated and life-threatening situations.

Prognosis. The prognosis for recovery after systemic candidiasis is much improved with better diagnostic and therapeutic approaches. The long-term outcome is apparently good but this needs more study. Intracranial (basal cistern) calcifications have been reported after recovery from Candida meningitis;[296] renal calcifications and decreased renal function have also been described after amphotericin B therapy.

Other Fungal Infections. Other fungal infections of newborns are extremely rare but can include histoplasmosis, cryptococcosis, phycomycosis, *Candida* (*Torulopsis*) *glabrate,*[361] and superficial dermatophyte infections. In endemic areas, coccidioidomycosis and other fungal diseases have also been reported. Occasionally, severely compromised newborns may have aspergillosis and other opportunistic fungal infections. Species of Candida other than albicans should not be dismissed as commensals when isolated in appropriate clinical situations. The clinical manifestations and the principles of diagnosis and management of these rare causes of infections in the newborn are similar to those in older subjects.

Enterovirus

The evidence for enterovirus (ECHO, coxsackie, polio) teratogenicity in humans is scant.[318] Study of this problem is hampered by the ubiquity of these agents, type-specific immune responses, nonspecific clinical manifestations, and subclinical infection. Intrauterine and perinatal infections probably occur more frequently than the literature would suggest.[257] Any enterovirus infection early in pregnancy may result in abortion or stillbirth.[153]

This group of viruses commonly infects the liver, heart, and brain and should be suspected in newborns with combinations of myocarditis (may present as cardiomegaly, arrhythmia, or pericardial effusion), hepatitis, and/or meningoencephalitis.[146] For diagnosis, the season (summer is "enterovirus season") and clinical features should be considered, as should exclusion of other possible causes of the clinical syndrome. The diagnosis can be confirmed by viral isolation from infected tissue (e.g., liver) or from CSF. Isolation of enterovirus from the respiratory or enteric tract of the mother or the infant, or serologic conversion, provides indirect evidence of infection.

Coxsackie. Some perinatally acquired enterovirus infections, such as coxsackie B, can be rapidly fatal or cause serious long-term sequelae secondary to CNS injury.[249] In other instances, subclinical infection or benign arrhythmias have been noted.[331] Clinical clues to the presence of this virus are: epidemiologic—presence of virus in community; maternal—pleurodynia in mother (or father); neonatal—myocarditis.

ECHO virus. ECHO virus infections can occur in utero[230] or postnatally.[255] What determines severity is unclear, but, as with coxsackie, both silent and fatal systemic viremias have been reported. Usually the mother has nonspecific malaise and fever with or without diarrhea. Two women had surgery for suspected appendicitis late in the third trimester; both proved to have echovirus 11 infections.[230,255] Perinatally acquired enterovirus can manifest in the newborn as a viremic syndrome with multiorgan involvement, indistinguishable from other causes of neonatal sepsis. Collapse, acidosis, and bleeding may be present.[54] Infants may also present with apnea, or other signs of CNS infections; this is a meningoencephalitis similar to that seen in older children during summer outbreaks. To an infectious disease specialist, apnea in a newborn in the winter suggests, among more common diagnoses, respiratory syncytial virus and, in the summer, enterovirus.

Poliovirus. Poliovirus can also infect the fetus and newborn with results similar to those described for the other enteroviruses; however, poliovirus infections are preventable nowadays.

Infants with enterovirus infection should be isolated (gown, handwashing, private area, if possible), as nursery outbreaks of enterovirus infection are possible.[329] No specific antiviral therapy is currently available. Management is supportive and may occasionally require pericardiocentesis for symptomatic pericardial effusions, digitalization, and treatment of arrhythmias. Many characteristics of congenital and neonatal enterovirus infections remain to be described.

Chlamydia

Maternal Infection. Chlamydial infections are usually sexually transmitted and are becoming more prevalent. Approximately one-half of the infants born to parents in lower socioeconomic populations have chlamydia antibodies in their cord blood.[379] This reflects maternal experience with this organism. Approximately 2–20% of females become infected during pregnancy. These infections are often asymptomatic but may also present as nonspecific urethritis, cervicitis, or pelvic inflammatory disease. Occasionally, peritonitis, perihepatitis, and acute salpingitis have been noted. Men may have epididymitis but, most characteristically, have a nongonococcal urethral discharge. If the mother has chlamydial colonization of the genitourinary tract at the time of delivery, approximately one-third of infants will acquire the organism during the delivery process.[12] In one recent survey, 22% of women in the third trimester harbored chlamydia and 28% of their newborns were positive by cultures. Ninety-five percent of these developed conjunctivitis and 17% developed pneumonia (together with conjunctivitis in one-third of cases).[209] Stillbirth and neonatal death rates are markedly increased in pregnancies complicated by maternal *Chlomydia trachomatis* infection.[293]

Intrauterine Infection. The consequences of primary maternal chlamydial infection during pregnancy are under intense investigation. It appears that fetal death may ensue with severe maternal infection and that prematurity may also be a consequence of infection in the third trimester.[203] The fact that intrauterine infection can occur is attested to by the experience with nine reported infants in whom *Chlamydia trachomatis* was cultured after they were delivered by cesarean section.[164] Three different syndromes have been reported under these circumstances, and these characterize chlamydial infections in newborns in other situations as well. These are (1) asymptomatic, (2) conjunctivitis, and (3) pneumonia with or without conjunctivitis.

Postnatal Infection: Clinical Manifestations. Since approximately one-third of infants exposed to mothers with chlamydial genitourinary infection will acquire the organism, it would seem there would be an overwhelming amount of neonatal chlamydial infection in the community. Yet these conditions seem less frequent in actual experience. Thus asymptomatic colonization or very mild infection must be the rule. I am sure we can also improve our clinical acumen.

Besides asymptomatic colonization, the most frequent manifestation of chlamydial infection in the newborn is conjunctivitis. This is usually seen within the first week of life but can occur up to the third week.[12] Recurrent or new infection may also account for the conjunctivitis seen with approximately one-half of the patients who develop pneumonia up to the third month of life. The conjunctivitis is characterized by a purulent exudate.[373] This can occasionally be confused with ophthalmitis due to silver nitrate or gonococcal infection.

Chlamydial pneumonia is most commonly seen in 6–12-week old infants who have a gradual onset of cough and tachypnea.[377] Rapid breathing is prominent, as is a prolonged cough (described as staccato), which is similar to the paroxysm of whooping cough but without the whoop. These infants are usually afebrile.

Diagnosis. Chlamydia organisms grow in tissue culture (usually treated McCoy cells) and require careful handling of specimens and rapid inoculation. Indirect evidence of conjunctivitis can be obtained by visualization of intracytoplasmic inclusions in epithelial cells scraped from lower palpebral conjunctiva and stained with giemsa. Chlamydia are usually isolated from the eyes in patients with conjunctivitis and also in those with pneumonitis, whether or not conjunctival inflammation is present. Thus, throat, nasopharyngeal, and conjunctival specimens, as well as lower respiratory secretions, are useful for isolation of chlamydia in infants with pneumonia. Pneumonia patients may also have increased serum concentrations of IgG and IgM and eosinophilia of greater than $300/\text{mm}^3$. Serologic confirmation of diagnosis requires the demonstration of a fourfold rise in titer between sera obtained during the acute illness and that obtained approximately 3–5 weeks later. The microimmunofluorescent test is most specific but the complement-fixation test is also useful, but may reflect cross-reactivity with other chlamydial antigens.

Treatment. Conjunctivitis is best treated with systemic erythromycin 50 mg/kg for 10–14 days.[210] Although the condition can be treated with tetracycline or erythromycin eye drops, neither eliminates respiratory colonization with the organism and relapse is possible. This is most marked, in fact, for sulfacetamide eye drops. Treatment of pneumonia is similar. The oral route is adequate; however, parenteral erythromycin may be prescribed in selected cases because of fatigue, dehydration, etc. Persistence of positive cultures should suggest the need to prolong therapy for up to 3 weeks in some infants with pneumonia. If cultures are not available, clinical guidelines should be used, but a minimum of 2 weeks therapy is recommended.

Prevention. Erythromycin eye ointment, used at birth, is the best preventative for chlamydial conjunctivitis.[193] Tetracycline, and sulfacetamide, are much less effective. Oral erythromycin can also be administered to mother during the week prior to delivery, should she have recognized chlamydial infection or colonization.[239] The prognosis in newborn infection is very good.

Acquired Neonatal Infections: Clinical Syndromes

Having considered congenital infections, let us now review infections acquired in the first month after birth. Those that occur predominantly in this age group will be presented in detail, whereas others also prevalent in older infants and children will be covered elsewhere. Factors that predispose to the frequency and severity of neonatal infection include premature delivery and prolonged rupture of membranes, maternal infections, difficult delivery, residence in a neonatal intensive care unit, use of fetal monitoring devices, and certain congenital anomalies. The latter may directly predispose the baby to infection, as in obstructive uropathy and meningomyelocele, whereas others indirectly increase risks if they require surgical procedures, use of indwelling catheters, parenteral alimentation, or respirators.

Neonatal Sepsis

Neonatal sepsis is widely diagnosed in newborns and therapy is initiated without exact knowledge of the cause in most cases. This is done because of the severe nature of bacterial infections in this age group and their rapid progression unless appropriate therapy is instituted early. Examples are early- onset group B Streptococcus infection, with up to 50% mortality rates, and fulminant listeriosis. Proven sepsis occurs in 1–10/1,000 live births, although the condition may be suspected in up to 60% of newborns in a neonatal intensive care unit.[403]

Pathogenesis. Maternal, neonatal, and environmental factors combine to create a favorable environment for invasive neonatal infections.[108] Maternal genitourinary infections,[479] prematurity in newborns with complicated predisposing conditions, and an environment replete with gram-negative pathogens and opportunists are examples of these contributing factors (Table 3-11). Add to this the busy traffic in newborn units and the many procedures that ill infants are exposed to (endotracheal suctioning,[429] respirators,[316] minor surgical procedures[243]) and one can begin to understand why nosocomial rates of 10–20% and a fertile environment for acquisition of new infection develop.[285] In such an environment, an infant who suddenly changes status is often considered to be septic, with appropriate diagnosis and treatment initiated swiftly.

Etiology. Many cases of suspected neonatal sepsis are later explained by metabolic or cardiorespiratory derangements. A small proportion have negative blood cultures initially, but evidence of localized bacterial infection later on.[414] Group B Streptococcus and *E. coli* account for the majority of proven cases of bacterial septicemia and are discussed in detail below (Table 3-12). *Staphylococcus aureus* and *S. epidermidis,*[45] *Listeria monocytogenes,* and Enterobacteriaceae are also seen and, less commonly, *Haemophilus influenzae,*[457] *Neisseria meningitidis,*[95] anaerobic bacteria,[86] and fungi may be responsible. Although group B streptococci are the most

TABLE 3–11. Maternal and Neonatal Factors Associated with Newborn Bacterial Infections

Maternal Conditions	*Effect*
Urinary tract infection	Prematurity, infection
Gram-negative bacterial infection	Neonatal distress, hypotension
Group B streptococcal infection	Septicemia, meningitis
Recurrent abortion	Listeriosis
Syphilis	Congenital syphilis
Prolonged rupture of membranes	Septicemia, pneumonia
Amnionitis, endometritis	Bacteremia, pneumonia
Coitus in last prepartum month	Chorioamnionitis
Newborn Conditions	*Effect*
Prematurity	Septicemia, meningitis
Hyaline membrane disease	Pneumonia
Congenital heart disease (L-R shunt)	Pneumonia
Urogenital abnormalities	Pyelonephritis
Intravascular catheters	Septicemia
Parenteral alimentation	Septicemia

TABLE 3-12. Causes of Neonatal Sepsis

- Bacteria
  - Group B *Streptococcus*
  - *E. coli*
  - *Klebsiella*
  - *S. aureus*
  - *Listeria monocytogenes*
  - *Streptococcus sp. pyogenes* and *pneumoniae*[347]
  - *Salmonella sp.*
  - Nontypable *Haemophilus influenzae*[457]
  - *Bacteroides sp.*
  - Anaerobic bacteria
- Viruses
  - Enterovirus (ECHO virus, coxsackie)
  - Influenza
  - CMV
  - Herpes simplex
  - Respiratory syncytial
- Fungi
  - *Candida albicans*

common Streptococcus causing neonatal septicemia, any group, including G[26, 127] and α-hemolytic (viridans) strains,[151] may do the same.

Clinical Manifestations. The clinical features of neonatal sepsis are nonspecific. Let us begin with the mother; when the mother has fever, diarrhea, vaginal discharge, and other signs of systemic infection just prior to, or during labor, neonatal sepsis should be presumed and appropriate investigations and treatments carried out in both mother and the infant. Prolonged rupture of membranes (> 12 h), maternal bacteremia, amnionitis, and other infections (e.g., endometritis) are also warning signals.

In the infant, prematurity, small size, asphyxia, poor apgar scores, hypotension, and signs of respiratory distress at birth should suggest the diagnosis of neonatal sepsis. Similarly, foul-smelling, bloody, or meconium-stained amniotic fluid, skin lesions, or funisitis (lesions or inflammatory changes in the umbilical cord) should alert us to this diagnosis. Later on, lethargy and poor feeding; hypothermia and hyperthermia in the absence of environmentally controlled temperature; and jaundice, vomiting, poor weight gain, abnormal cry and tone, acidosis, and a variety of skin rashes should also suggest the diagnosis. Other physical signs include bleeding (on the basis of diffuse intravascular coagulation or immune thrombocytopenia[435]) and more obvious features of infection such as skin abscesses, conjunctivitis, diarrhea, and omphalitis. Abnormal urinary sediment and CSF may suggest specific diagnoses as well. Fever in newborns is rare, but should be considered highly likely due to bacterial infection in full-term infants.[455]

Clinical manifestations may also reflect other features of neonatal sepsis, namely hemolysis, thrombocytosis, acidemia, hyperkalemia, hyponatremia, and specific organ dysfunction (depending on the site of focal infection or toxic effects of the infecting microbe).

Diagnosis. The first element in the diagnosis of neonatal sepsis is suspicion. This is heightened by some of the facts outlined above for maternal, neonatal, and environmental factors and during outbreaks of nosocomial infection.

Appropriate bacterial cultures obtained before administration of antibiotics are essential for accurate management.[290] In almost all cases this should consist of blood, CSF, and urine. Similarly, conjunctival, skin, endotracheal, and rectal swabs or stool should be examined in patients with signs of involvement in those areas. When maternal factors point to intrauterine or ascending infection, examination of maternal and placental material,[236] amniotic fluid,[479] umbilical cord, and the infant's ear and gastric aspirates are also useful.[134] The latter two should be carried out before 12 h of life and results need to be interpreted cautiously, in consideration of the fact that vaginal and perineal flora may often be reflected in ear and gastric cultures. However, the presence of many polymorphonuclear leukocytes and bacteria on gram stain should be taken seriously. The blood buffy coat can also be examined with methylene blue or gram stain. This may provide rapid evidence of bacteremia and, occasionally, fungemia. Aerobic and anaerobic blood cultures are important. For example, candidemia and Pseudomonas bacteremia are best diagnosed by blood culture in aerobic media while clostridia and Bacteroides grow only in an anaerobic environment. Blood cultures should be obtained by venipuncture after careful antiseptic preparation of the skin; blood obtained via the umbilical artery or vein, and from capillary sites, is often contaminated.[19,287] Since staphylococci are not an uncommon cause of neonatal sepsis, particularly in outbreak situations, a skin swab obtained after antiseptic preparation of the site for blood culture may be useful in assisting the interpretation of results.

Viral Sepsis. Since viral infection (e.g., enterovirus, influenza) may be responsible for some cases of neonatal sepsis, appropriate cultures should be taken in infants with relevant exposure history. Positive results may be extremely helpful. For example, isolation of respiratory syncytial virus may explain apnea; coxsackie, a case of myocarditis; and an ECHO virus may clarify signs suggestive of sepsis.

Nonmicrobiologic Clues to Sepsis. Several nonmicrobiologic tests have correlated with the presence of sepsis. These include white blood cell counts of < 5000/mm³, bands/total neutrophils ≥ 0.2, latex C-reactive protein of > 0.8 mg/100 ml,[11] erythrocyte sedimentation rates of ≥ 15 mm/h in the first hour, and latex haptoglobin of > 25 mg/100 ml. Using these criteria, Philips et al. reported 39% of patients with two or more positive results had sepsis;[348] the exact etiology is, of course, dependent on microbiologic testing. In situations where antibiotic overuse is a real problem, the application of such tests, in addition to the history and clinical finding, can be used to effectively limit the numbers and duration of antibiotic therapy in certain cases.

Once sepsis has been documented, sources of bacteremia should be carefully sought. The search for foci such as abscess or endocarditis have been made easier by the advent of echocardiography, ultrasonography, and radionuclide scans.

Treatment. In most cases of suspected sepsis, no microbiologic confirmation will be evident, and a plan for discontinuing antibiotics after 48–72 h is recommended.[415] Use of clinical and nonmicrobiologic clues is helpful.

Most commonly, a combination of β-lactam and aminoglycoside antibiotics (Table 3-13) is used, in recognition of the most frequent causes of neonatal sepsis, i.e., group B Streptococcus and *E. coli.*[291] It is obvious that not all pathogens can be covered effectively by this regimen, and, in certain situations, different antibiotic combinations should be chosen. An example is treatment of sepsis during a nursery outbreak of gentamicin-resistant Klebsiella. Use of microbiologic surveillance is helpful in determining the frequency of certain pathogens and their antimicrobial susceptibility patterns. "Ten Commandments" for the use of antibiotic therapy in newborns are listed in Table 3-14.

Adjuncts to antimicrobial therapy of neonatal sepsis include exchange[449] and granulocyte transfusions.[92] The former is used in patients with hypotension, electrolyte and acid-base derangements, and coagulopathies. It is one of the most rapid ways to adjust one or more of these abnormalities and at the same time provide opsonins, immunoglobulin, fresh leukocytes, clotting factors, and perhaps even wash out bacterial toxins and bacteria from the newborn's bloodstream. Granulocyte trans-

TABLE 3-13. Initial Therapy of Neonatal Sepsis

Suggested Antibiotic Regimen
Ampicillin, IV: 50–100 mg/kg/day divided q 12 h for first week of life. Then 150–200 mg/kg/day q 6–8 h
Gentamicin, IV or IM: 5 mg/kg loading dose. Then 5 mg/kg/day divided q 12 h for first week of life, then 6–7.5 mg/kg/day divided q 8 h. Use 2.5 mg/kg q 18 h in neonates < 34 weeks of age.

TABLE 3-14. Antibiotic Therapy in Newborns

1. Antibiotic susceptibility pattern in a specific nursery (an obstetric, perinatal unit) may suggest alternate programs to the one in general use.
2. Outbreak of nosocomial infections may require specific antibiotic regimen for initial therapy of neonatal sepsis.
3. Colonization surveillance may reveal predominant microbial flora in high-risk neonate. Suspected sepsis in such an infant should include antimicrobials active against these flora.
4. Discontinue antibiotics if cultures are negative at 48 h, unless focal infection is diagnosed (e.g., pneumonia, deep abscess).
5. Monitor serum (other body fluid) concentrations and/or activity of antibiotics in proven infections.
6. Monitor serum concentrations, and adjust dose/frequency of aminoglycosides and chloramphenicol daily, if therapy is prescribed for more than 48 h (in certain situations, these drugs will require monitoring after the first dose, e.g., renal failure, liver dysfunction, very immature infant, proven infection).
7. Administer 2 ml prophylactic nystatin 100,000/units ml orally six times daily in high-risk newborns receiving antibiotics for more than 48 h.
8. Repeat cultures to determine time of bacteriologic eradication and in vivo efficacy.
9. Alter dose and frequency of antibiotic as the infant's organ function changes (e.g., liver for chloramphenicol, kidney for aminoglycoside).
10. Survey microbial flora in high-risk newborn receiving antibiotic therapy, since risk of superinfection is great.

fusions may be useful in neutropenic septic newborns, although experience with this approach is limited.[93] Certainly, cardiorespiratory support, correction of electrolyte and acid-base abnormalities, and optimal nutritional management are indicated.

Most infants with neonatal sepsis need not be isolated unless specific indications are at hand. One exception may be infants colonized by highly resistant and/or virulent bacteria where the risk of spread is great and the consequences of infection might be disastrous. This is well illustrated by a recent nosocomial outbreak of *Serratia marcescens* infection traced to contaminated handwashing brushes.[18]

Prognosis. The outcome of neonatal sepsis is usually dependent on the specific cause. Overall, the mortality rate is approximately 30%; however, the majority of survivors do well. Because the condition is most prevalent in the youngest, smallest infants with serious underlying conditions, the final outcome is dependent on many factors. In one survery, 22% of survivors had major handicaps.[16] Abscesses or other foci, such as arthritis, osteomyelitis, or endocarditis should be looked for in patients with persistent bacteremia or slow clinical response despite appropriate antibiotic therapy. For example, hepatic abscesses may be present in sepsis associated with vessel cannulation or abdominal surgery.[321] Hydrops of the gallbladder can also be seen.[346] In the final analysis, this is a condition that must be diagnosed quickly and treated before a specific cause is outlined. The importance of prevention of neonatal sepsis by detection and appropriate therapy of maternal and perinatal complications is self-evident.

Meningitis

Etiology. Bacterial meningitis in the newborn is different in several respects. First of all, the causative organisms are different. Group B Streptococcus, *E. coli,* Listeria, Citrobacter, Klebsiella, α-hemolytic Streptococcus,[151] Salmonella, and Enterobacter[244,326] are usually responsible. Unusual causes, such as *Plesiomonas shigelloides,*[344] *Vibrio cholerae,*[374] and *Flavobacterium meningosepticum* may create difficult diagnostic and treatment problems.[85] Bacteria invade the meninges as part of a bacteremic syndrome that may also involve other organs. Approximately one-quarter of newborns with sepsis also have meningitis.[451] Secondly, antibiotic therapy is seldom successful in eradicating the bacteria from the CSF in less than 4 days.[297] Group B Streptococcus, *S. pneumoniae,* and Listeria may be eliminated more rapidly (within 24–48 h) in some infants. Finally, mortality and acute long-term morbidity rates are more pronounced at this age.

Candida meningitis is rare, but can be successfully treated with a combination of amphotericin B and 5-fluorocytosine.[277] *Mycoplasma hominis* frequently colonizes the maternal genital tract and is a rare cause of neonatal infection, including meningitis.[212,303]

Clinical Manifestations/Diagnosis. The clinical features of neonatal meningitis can usually be summarized in one word: nonspecific, and the diagnosis in two: lumbar puncture. Admittedly, some signs of meningitis are highly suggestive (e.g., apnea, seizures, bulging anterior fontanelle, extreme lethargy and irritability), albeit late. More commonly, poor feeding, vomiting, loss of muscular tone, fretfulness, or hypothermia may be present, signs difficult to ascribe specifically to meningitis. Hence there is a need for including CSF examination and culture in all cases of suspected neonatal sepsis. Specific aspects of the diagnosis of *E. coli,* group B Streptococcus, and *Listeria monocytogenes,* common causes of neonatal bacterial meningitis, are outlined elsewhere in this chapter.

Ventriculitis, with or without acute hydrocephalus, may be present early in neonatal bacterial meningitis. Clues include severe encephalopathic signs, bulging fontanelle, widened sutures, focal neurologic signs, and recurrent or persistent seizures. Baseline measurements of head circumference, transillumination, and a computerized axial tomogram should be obtained. The latter is used to outline the size of the ventricles and to define the presence of ventriculitis, hemorrhage, brain atrophy, or abscess. A ventricular tap should be performed if signs of ventriculitis or noncommunicating hydrocephalus are present. CSF so obtained can be used for assessment of inflammatory changes, culture, and measurement of antibiotic concentrations. The need for drainage or alterations in antibiotic therapy may thus be defined.

Treatment: General. Current therapy programs recommended for treatment of group B Streptococcus, *E. coli*, etc. are appropriate for meningitis. High dosages are recommended because of the poor penetration of many of these drugs into the CSF. Intrathecal and intraventricular routes have been tried but have not improved the outcome of neonatal meningitis.[297,298] Adequacy of antibiotic therapy should be assessed by comparing CSF antibiotic concentrations with the quantitative susceptibility of the infecting bacteria. Alternatively, CSF and serum inhibitory and killing titers can be used to monitor in vivo therapeutic efficacy.

Therapy should be continued after sterilization of the CSF for at least 1 week for gram-positive, and 2 weeks for gram-negative bacteria, but for a minimum of 2 weeks for gram-positive, and 3 weeks for gram-negative meningitis. These infants require a team approach to handle the complications and systemic manifestations of their bacteremia and meningitis syndromes. Isolation is usually not indicated, but nursery outbreaks of meningitis have been reported.[170,208] Since neonatal meningitis is such a rarity, two or more cases in a nursery warrant isolation and epidemiologic study.

Treatment: Specific Causes. It is particularly important to examine each isolate of group B Streptococcus and Listeria for tolerance to penicillin.[404] If this is found, both ampicillin (preferred over penicillin because of its superior penetration into the CSF) and amikacin (also penetrates inflamed CSF well)[480] should be used for a minimum of 2 weeks.

E. coli K1 is the antigenic type of *E. coli* responsible for most cases of meningitis. Although the pathogenesis of this infection has not been completely elucidated, these organisms are usually susceptible to combinations of β-lactam and aminoglycoside drugs. Third-generation cephalosporins, such as cefotaxime, can be considered for therapy in these patients as well.[389]

Citrobacter diversus is an occasional cause of bacteremia and meningitis in newborns, and is characterized by development of brain abscesses.[171] Although sensitivities of this organism vary, chloramphenicol or trimethoprim/sulfamethoxazole may often be useful,[174] as may moxalactam.[273]

Rare causes of meningitis may also be seen in these immunologically immature hosts. These include *Bacteroides fragilis*, which may begin as a scalp abscess and progress to meningitis. We treated one case with metronidazole with an excellent result.[265]

Complications. These infants are particularly prone to development of acute hydrocephalus, seizures, deafness, and blindness. These complications should be anticipated and looked for early in newborns. CSF should be examined at least daily until sterilization has been demonstrated. Patients resistant to antibiotic therapy, and those with progressive signs, should have repeated computerized axial tomography and other examinations appropriate for the diagnosis of ventriculitis, subdural effusion or empyema, brain abscess, or cerebrovascular thromboses. Transillumination, head circumference measurements, and ventricular and subdural taps are useful in this age group.

Prognosis. The prognosis for neonatal meningitis is still poor. Approximately 15–20% of these infants die in the early acute phase of their illness. A smaller percentage die during early and late convalescence. As many as one-half of all survivors have moderate to severe neurologic or neuropsychologic abnormalities. The necrotizing and hemorrhagic injury of meningitis in newborns can result in polycystic degeneration,[72] hydrocephalus[244] and diverse manifestations of neural dysfunction—e.g., hypothalamic-pituitary disturbances.[338] Ventriculitis is present in about three-quarters of newborns with gram-negative enteric meningitis. This is correlated with a poor prognosis, as is persistence of positive CSF cultures beyond 3 days, CSF white blood cell counts above 10,000/mm^3, and a CSF protein of above 500 mg/dl.

Respiratory Infections

Many of the specific syndromes associated with respiratory infections in newborns have been described in detail in previous sections. The newborn is also susceptible to many respiratory infections that will be discussed under appropriate sections for older patients. However, there are some special features of neonatal respiratory infection that deserve emphasis. During delivery, aspiration of meconium, blood, other debris, and a diversity of microbiologic flora may occur and further compromise the infant's immature respiratory defenses. For example, IgA is relatively deficient in respiratory secretions, and mucociliary excretion mechanisms are incompletely developed. Add to this the toxic effects of oxygen[57] and the use of mechanical ventilation, and it is indeed remarkable that more respiratory infections are not documented during the first few days of life. Amniotic fluid, among other factors, seems to protect the fetus and newborn well, for microbiologically positive cases of congenital[318] and aspiration pneumonia[456] in newborns are rare.

Etiology. Some of the common causes of respiratory infection in newborns are outlined in Table 3-15. Foci of inflammation and gram-negative bacteria are present in the lungs of almost one-half of autopsied newborns but rarely do these represent true congenital or perinatal pneumonia of any consequence.[43]

Generally mothers and other caretakers with respiratory infections are the reservoirs for viral respiratory infections in exposed infants.These may manifest as upper respiratory infection, common cold syndrome, pharyngitis, or rhinitis in adults but may lead to pneumonia in the newborn. Similarly, conjunctivitis or diarrhea in the mother may be reflected by pneumonia due to adenovirus or coxsackie virus in the infant, respectively. Other examples include CMV infection in mother which may have presented during pregnancy as a mononucleosis-like syndrome, asymptomatic cervical infection, or urinary shedding. As a result the infant may manifest pneumonia as part of a generalized intrauterine, or postnatally acquired, CMV syndrome. A newborn syndrome characterized by pneumonia, thrombocytopenia, and hepatomegaly can also be due to CMV acquired by blood transfusion.[476] Chlamydia infection may cause urethritis or asymptomatic colonization of the genitourinary tract in the mother, but pneumonia with or without conjunctivitis in the infant. Most respiratory infections acquired by the mother during pregnancy are of little consequence. Although influenza has been blamed for abortion and premature labor, transplacental spread is rare.[362]

Several points deserve emphasis. Once home, newborns rarely acquire gram-negative bacillary pneumonia. Exceptions are infants recently (within 2–3 days) discharged from an intensive care nursery and malnourished infants (particularly prone to *Staphylococcus aureus*). In other newborns, bacterial causes of pneumonia are similar to those seen in older infants, i.e., *Streptococcus pneumoniae* and *Streptococcus pyogenes* and,

TABLE 3–15. Common Causes of Respiratory Infection in Newborns

- Viral
  - Respiratory syncytial
  - Parainfluenza
  - Influenza
  - CMV
  - Adenovirus
- Bacterial
  - Group B Streptococcus (*Streptococcus agalactiae*)
  - *E. coli*
  - *Listeria monocytogenes*
  - *Bordetella pertussis*
- Other
  - *Chlamydia trachomatis*

less commonly, *Staphylococcus aureus* and *H. influenzae*. The majority of respiratory infections of newborns, in and out of the hospital, are due to viruses.

Clinical Manifestations. Respiratory infections in newborns take on several different presentations. Most cases present in a nonspecific fashion, similar to neonatal sepsis and many of the bacteremic and viremic syndromes, i.e., pallor, poor feeding, tachycardia, and tachypnea may be indications of respiratory infection.[188] As such, respiratory involvement may be only part of a generalized syndrome, as with group B Streptococcus infection.

Other neonatal respiratory infections have more characteristic presentations (Table 3-16). Apnea in the newborn is often considered a manifestation of CNS or cardiovascular dysfunction. However, apnea may also be a feature of respiratory syncytial virus infection;[20] drowsiness, hypotonia, and seizures have also been reported in these infants.[320] Rarely, respiratory syncytial virus infection in newborns may result in fever with rash.[448]

Rhinitis, cough, and the classic symptoms of upper respiratory infection in older children are frequently seen in newborns. When present, they may indicate infection with common respiratory viruses or chlamydia and lower respiratory involvement should be suspected. Although paroxysmal coughs are described in this age group,[289] pertussis may more commonly present in the newborn as a consolidated pneumonia with atelectasis and

TABLE 3-16. Clinical Manifestations of Respiratory Infections in Newborns

Presenting Feature	*Probable Cause*
Respiratory distress syndrome	Group B Streptococcus
Apnea	Respiratory Syncytial Virus
Tachypnea	Chlamydia
Cough Staccato	Chlamydia
Paroxysmal	Pertussis
Associated Features	
Mycocarditis	Coxsackie B virus
Hypotension	Group B Streptococcus
Rhinorrhea	Parainfluenza, Rhinovirus
Diarrhea	Enterovirus
Thrombocytopenia/hepatomegaly	Cytomegalovirus
Pustules	*Staphylococcus aureus*
Conjunctivitis	Chlamydia/Adenovirus
Contact with sick bird	Psittacosis

severe congestion. Feeding difficulty, choking, or apnea are often noted, with very little cough and no whoop.[98]

Diagnosis. Respiratory infection in the newborn, when suspected, should be dealt with as aggressively as infection in any other system. Rapid respiratory compromise and the risk of nosocomial spread justify this approach. Upper respiratory signs in the newborn should prompt an examination of the lower respiratory tract. This almost always includes a chest X-ray. This is especially important in newborns because of the difficulty of eliciting signs in this age group that may indicate the presence of consolidation, pleural effusion, pneumatocele, atelectasis, or pneumothorax.

Appropriate examination and culture of respiratory secretions are also very important. The newborn is an excellent candidate for direct laryngoscopy and tracheal aspiration. After all, this procedure is frequently performed for resuscitation of the newborn and for many other indications. Why not for the diagnosis of lower respiratory disease? Fluid obtained directly from the subglottic tracheo-bronchial area can be used for gram smear (or other stain, if appropriate) and cultured for bacteria, viruses, chlamydia, etc. Upper respiratory secretions are also useful for respiratory viral cultures, urine for CMV, and stool for enterovirus and adenovirus. The presence of pneumonia means that a blood culture is necessary and that lumbar puncture, urine culture, and examination for other evidence of generalized sepsis should be carried out. Indirect evidence of bacterial infection can be acquired by use of diagnostic methods for detection of bacterial antigens. Examination of the urine for Haemophilus, pneumococcal, and group B streptococcal antigens is an example.

In certain situations other procedures are indicated. When pleural effusion is detected, thoracentesis is mandatory. Considering the spectrum of causes of empyema and pleural effusion in newborns, the opportunity to examine and culture this fluid should not be lost. In other situations, progressive pulmonary involvement despite apparently appropriate therapy and other supportive management should prompt consideration of precutaneous needle aspiration or open lung biopsy. These are useful for diagnosing *Pneumocystis carinii* infection and tuberculosis and may be essential to rule out the presence of fungi and resistant and unusual bacteria, or to confirm a diagnosis of influenza or adenovirus pneumonia.

Pneumocystis carinii is a rare pathogen in newborns although nursery outbreaks have been reported.[156] These protozoa can also be associated with CMV or chlamydia pneumonia.[197] Confirmation of its presence is critical in newborns, considering its rarity and the potential toxicity of treatment with either trimethoprim/sulfamethoxazole or pentamidine isethionate in this age group.

Therapy. Treatment of respiratory infections in the newborn is similar to that in other age groups. Supportive therapy for hypoxemia, carbon dioxide retention, acid-base and electrolyte imbalances, and other disturbances associated with respiratory infection is indicated. Postural drainage, gentle suctioning, and nutritional support should not be forgotten.[140]

Suction of the nares with a soft rubber bulb or aspirator before feeding is very helpful. Nose drops, cough medications, decongestants, and cold remedies should not be prescribed for these patients. Rebound congestion, extreme sensitivity to side effects, and interference with normal clearance mechanisms are some of the reasons for this advice.

Specific antimicrobial therapy depends on clinical and microbiologic diagnoses. Since pneumonia is rarely an isolated phenomenon, treatment should follow many of the guidelines outlined for sepsis. Influenza pneumonia in newborns should be treated with amantadine 5 mg/kg/day, divided q 12 h.[207] Ten to fourteen days of therapy is recommended for most bacterial pneumonias. Evidence for microbiologic cure should be obtained if possible. An additional week of therapy beyond that point should suffice for most pneumonias. Complicated cases, such as those with empyema, extrapulmonary involvement, or lung abscess, require longer durations of therapy. Chlamydia pneumonia should be treated with erythromycin for 3 weeks, because of the difficulty of eradicating the organism and the danger of spread and relapse. Tuberculosis is another exception, requiring a minimum of 9 months of therapy in most cases.

Prevention. The most effective way to avoid catastrophies associated with severe respiratory infection in newborns is prevention. Hence it is foolhardy to allow caretakers with obvious respiratory infection to handle newborn infants. The common cold syndrome in an adult may become life-threatening pneumonia in the infant. Although breast-feeding may not reduce the frequency of respiratory infections, the severity may be diminished.[150]

The identification of a communicable respiratory infectious syndrome in a newborn is an indication for appropriate isolation procedures. Clear examples are provided by newborns with pertussis, tuberculosis, and the adenovirus pneumonias. Isolettes are not appropriate isolation for these children. Private rooms or facilities where the ventilation can be controlled to decrease the risk of aerosol spread should be sought. Although the role of masks is controversial, they are probably indicated when caring for patients with pertussis or influenza. A confirmed diagnosis of respiratory syncytial virus infection should allow relaxation of the need for masks.[187] In all cases, handwashing is of the utmost importance. Extension of this advice to home situations is also useful. Practitioners should remind parents to avoid exposing their new infant to respiratory infection as much as feasible. The newborn is particularly distressed by congestion of the airways and tires easily during feeding when secretions fill the nose and nasopharynx. Rarely is this life-threatening, but occasionally it can be. More commonly, it is a source of anxiety and distress for baby and family, leading to sleepless nights for both. Influenza may be prevented in newborns by predelivery immunization of the mother before or during pregnancy.[358]

Prognosis. Generally excellent, the prognosis takes on more serious tones in babies with underlying pulmonary conditions, such as bronchopulmonary dysplasia and recurrent aspiration syndromes, and in infants with congenital heart disease.[161] Repeated respiratory infection can add structural and hemodynamic stresses that may become life-threatening. Adenovirus, endobronchial tuberculosis, and, possibly, severe pertussis may be followed by endobronchial fibrosis with recurrent atelectasis, pneumonia, and bronchiolitis obliterans.[473] Fortunately, these are rare sequelae.

Urinary Tract Infection

Unlike the situation in older patients, urinary tract infections in newborns are usually associated with bacteremia and are more common in males than in females. A survey of 1762 high-risk newborns found significant bacteriuria in 2.4% with a male-to-female preponderance of 5:1.[286]

Clinical Manifestations/Diagnosis. Some newborns are completely asymptomatic, while others manifest vomiting, jaundice, diarrhea, and weight loss. In newborns, urinalysis often correlates poorly with the presence of urinary tract infection.[128] Bacteriuria should be defined by means of a suprapubic bladder aspiration in most cases. Rarely, a true midstream "catch," or urine obtained at surgery directly from ureter or kidney can be used. Urine cultured from bags and other attached urine collection devices are notoriously unreliable in newborns. False-positives (as compared with urine cultures obtained by bladder aspiration) have been as frequent as 50%.[363] Although the gram stain can be used as a rapid screen for quantities of bacteria $> 10^5$ colonies/ml, any quantity of bacteria cultured from the bladder is significant. Blood culture and examination of the CSF are indicated in almost all cases of newborn urinary infection, since bacteremia is so commonly part of the pathogenesis.

Treatment. *E. coli* is the most common cause, although Klebsiella, Proteus, *Streptococcus fecalis,* Staphylococcus, and mixed infections also occur. Hence, initial therapy should include ampicillin and gentamicin or an equivalent combination of antibiotics; this can be adjusted after culture and appropriate sensitivity testing. The duration of therapy should be a minimum of 2 weeks or 7–10 days after bacteriologic sterilization and clinical improvement.

Prognosis. As with older subjects, reflux may be present in the acute stages of infection in the absence of congenital anomalies or obstruction. In fact, newborns have been reported with hydroureteronephrosis that spontaneously resolved after medical management.[339] Thus a conservative approach appears warranted, before consideration of surgery in such cases, unless an obvious cause of obstruction is present. Recurrences can be seen within the first 3 months of life, but are infrequent thereafter, again unlike the situation in older children.[51]

Osteomyelitis/Arthritis

Etiology. Osteomyelitis and septic arthritis are rare in newborns and not easily diagnosed.[351] Predisposing conditions include bacteremia, venipunctures, heel stick for blood sampling,[276] cephalohematoma,[133] and umbilical artery catheterization.[278] *Staphylococcus aureus,* group B Streptococcus, and gram-negative enteric bacilli are important causes; unusual invaders include anaerobes and fungi. Causative pathogens are frequently present on the skin and umbilicus of infected infants and may invade through indwelling umbilical catheters.

Metaphyseal foci develop early and spread quickly across the growth plate along transphyseal vessels. Adjacent septic arthritis may thus occur.

Diagnosis. Radiographic changes may be seen as early as 5 days after infection of the bone by both hematogenous and direct routes. Radionuclide scans with technetium or gallium may be positive before X-ray changes; cultures of blood and material aspirated directly from the bone and/or wound material are most helpful.

Treatment. In general, these infections are amenable to medical management although recovery may be hastened by surgical debridement of skull and poorly vascularized areas. Objectives of therapy include sterilization of the bone (and wound, if present); improvement in nonspecific signs, such as appetite, weight gain, activity, erythrocyte sedimentation rate, and fever; and radiographic evidence of healing. Principles of therapy are the same as in older infants and children, although particular attention should be paid to the pharmacokinetics of the antibiotics used, in consideration of the paucity of experience with many of these drugs in newborns. Efficacy of therapy should be monitored by appropriate serum killing activities, bacteriologic surveillance of the infected site, and surveillance for adverse effects due to the antibiotic treatment. These principles hold true regardless of the route of administration of drug, our bias being to treat the patient by the oral route if drug absorption can be shown to be adequate and patient compliance ensured. Antibiotic resistance is commonly encountered in nursery populations, including methicillin-resistant staphylococci[460] and multiply-resistant Enterobacteriaceae. A 4-week course of therapy may be sufficient, although an effort should be made to treat these infections for approximately 2 weeks after sterilization and stabilization of clinical signs. Full recovery of joint function is usually reported.

Diarrhea

Bacterial Etiologies. When mother has diarrhea in the perinatal period, viral and bacterial causes are common and infection of the newborn is frequent.[109] Environmental sources and caretakers are also important in the spread of neonatal diarrhea. Salmonella or Shigella are particularly hazardous to the infant because of the risk of bacteremia and extragastrointestinal infection and the prevalence of antibiotic-resistant strains.[218] Thus, knowledge of the etiology of mother's diarrhea or febrile episode may be lifesaving for the infant. Microscopic examination and culture of the infant's stool, gastric aspirate, and blood buffy coat may also provide early clues to etiology. Neutrophils in the stools are common with shigellosis, pseudomembranous colitis, and in early Salmonella enterocolitis.[201]

Campylobacter and Yersinia are uncommon causes of neonatal diarrhea in North America probably because of the rarity of carriage of these bacteria in adults and the lack of exposure to contaminated food and animal reservoirs. *E. coli* can cause epidemic diarrhea in nurseries and should be suspected in outbreaks.[232] Quantitative cultures and serotype identification can be helpful in ascribing cause. Many such strains lack the characteristics of invasiveness and enterotoxigenicity, yet still cause diarrhea.[272]

Cholera, if severe in the mother, may lead to abortion or premature onset of labor. Neonatal cholera is rare, probably as a result of maternal immunity transferred to the infant predominantly via breast milk.

It is unclear whether enteric bacilli, such as Klebsiella, Enterobacter, Proteus, and Pseudomonas cause diarrhea in newborns. *Staphylococcus aureus* and *Candida albicans* need to be considered in a similar fashion. When these organisms are present in large numbers in the stool of symptomatic babies in whom the other known causes of diarrhea are excluded (including pathogenic bacteria, viruses, amebae, antibiotics, etc.), a pathogenic role is possible and specific antimicrobial therapy seems appropriate, along with supportive therapies and isolation. Antibiotics, severe debilitation, underlying gastrointestinal disease, or specific exposure contribute to the pathogenesis of these acquired diarrheas.

Viral Etiologies. Viral causes of neonatal diarrhea are becoming more apparent as diagnostic procedures improve.[450] Thus, rotavirus has been implicated in nursery outbreaks of diarrhea;[324] however, surprisingly large numbers of asymptomatic excretors have also been found.[94] This creates a difficult problem with regard to isolation, which may have to include cohorting both symptomatic and disease-free, but colonized, infants. Diagnosis is made by viral culture of stool or rectal swab specimens and demonstration of rotavirus or adenovirus particles by electron microscopy or antigen by ELISA methods. Other causes of neonatal diarrhea are similar to those encountered in older patients (see Chapter 6). If there is no history of exposure and the newborn baby appears to be the only case of diarrhea, consideration of noninfectious causes is recommended.

Treatment. Antibiotic therapy is indicated for most cases of neonatal diarrhea due to recognized enteric bacterial pathogens (Table 3-17). This is because newborn immune defense mechanisms are immature and susceptibility to extragastrointestinal complications is increased in these pa-

TABLE 3-17. Therapy of Neonatal Diarrhea

General
Fluid[191,352]
Electrolytes
Calories
Isolation
Antibiotic
Salmonella/Shigella
Ampicillin IV 150 mg/kg/day divided q 12 h in first week, q 8 h in second week and q 6 h thereafter.
or
Chloramphenicol 25 mg/kg/day PO in first 2 weeks, then 50 mg/kg/day q 12 h thereafter.
Campylobacter fetus
Erythromycin ethylsuccinate PO 40 mg/kg/day divided q 12 h.
Yersinia enterocolitica
Gentamicin 5 mg/kg/day IM or IV divided q 12 h in first week, then q 8 h.
E. coli
Neomycin 50 mg/kg/day PO divided q 6 h × 3 days

tients. For example, Salmonella are capable of infecting newborns rapidly and in small numbers because of the relatively alkaline pH of the stomach and the paucity of normal gastrointestinal flora in the first few days of life. In some cases both parenteral and oral nonabsorbable antibiotics are required to hasten recovery. An example is the baby with persistent Salmonella gastroenteritis with mucosal ulceration and systemic invasion despite appropriate parenteral antibiotics. Sulfonamides should be avoided in the first 2 weeks or any time hyperbilirubinemia is present in the newborn period. Chloramphenicol concentrations should be monitored to avoid toxicity.

Treatment of *E. coli* and other bacterial causes of gastroenteritis is dependent on susceptibility patterns. *E. coli* can usually be treated with colistin or neomycin by mouth for 3 days.[332] Enteric isolation techniques (particularly scrupulous handwashing) are needed to curtail spread in all cases.

C. difficile and Antibiotic-Associated Diarrhea

As mentioned above, diarrhea may be a sign of noninfectious problems as well. This can be drug-induced, as exemplified by antibiotic-associated diarrhea. At first it appeared that the pathogenesis of this condition in newborns had been dicovered by extrapolation of new knowledge about *Clostridium difficile* and the role its toxins play in pseudomembranous and antibiotic-associated colitis of adults.[120] Alas, the explanation is not that simple, since several reports have documented pseudomembranous colitis associated with *C. difficile* in infants who never received antibiotics[8] and, even more striking, *C. difficile* and its toxins are present in the stools of many asymptomatic normal newborns.[119] The role of this organism in the pathogenesis of necrotizing enterocolitis, another idiopathic type of neonatal diarrhea, is also unclear.[392]

Necrotizing Enterocolitis

Diarrhea in newborns might also herald the onset of necrotizing enterocolitis in the appropriate host, i.e., prematures with past episodes of hypoxemia, those receiving antibiotic therapy, and those with other predisposing factors are particularly at risk.[245] Clinical features include abdominal distention, bloody diarrhea, and, later, pneumatosis intestinalis (radiographic visualization of gas in the bowel wall).

Etiology/Pathogenesis. The role of bacteria in the pathogenesis and course of necrotizing enterocolitis is unclear. Clustering of cases, apparent cessation of spread with cohorting,[60] and predominance of certain bacteria in specific outbreaks e.g., *Enterobacter cloacae,*[355] *Clostridium butyricum,*[430] *Clostridium difficile,*[80] and enterotoxigenic *E. coli*[107]) suggest that bacteria and/or other infectious microorganisms (e.g., coxsackie B,[226] coronavirus,[87] and rotavirus,[371]) play an important role in the pathogenesis and spread of this condition. Whether this is in fact an infectious disease with many causes, or a syndrome in which certain organisms act as triggering events or as secondary invaders, is unknown. Certainly, bacteremia appears to be a secondary event in this disease.

The role of *Clostridium difficile* and its toxin in necrotizing enterocolitis is also unresolved. Both have been found with surprising frequency in infants with necrotizing enterocolitis. Lacking prospective examinations of such infants, however, it is unclear whether this is a cause or an effect of the condition. The situation is complicated by the fact that the gastrointestinal flora in asymptomatic newborns also includes *Clostridium difficile* and/or one of its enterotoxins. These strains and toxins isolated from well newborns are indistinguishable from those seen in sick infants. Nevertheless, it is probable that *C. difficile* may be the responsible agent in some outbreaks of necrotizing enterocolitis.[194] Bacterial surveillance in nursery intensive care units is important in making such judgments.

Currently, understanding of this disease indicates that specific hosts, predisposed by certain conditions, are likely to develop diarrhea due to nosocomially acquired gastrointestinal flora; several different bacteria in these flora seem capable of contributing to the condition. Those that elaborate enterotoxins or other necrotizing enzymes seem most likely to be pathogenic in this condition. Although endotoxemia has been described in the blood of these patients,[383] its presence, like bacteremia, is probably a secondary event representing a breakdown of the normal defenses offered by intact gastrointestinal mucosa.

Treatment. Since the gastrointestinal tract is severely ulcerated, and at times even perforated, aggressive medical management includes broad-spectrum antibiotics that are active against the bacteria mentioned above. Such a program could include ampicillin and gentamicin or tobramycin, or other combinations of β-lactam and aminoglycoside drugs. The addition of topical (oral) gentamicin appears to offer no advantage.[196] Vancomycin may be useful in outbreaks associated with *C. difficile* colonization, although prospective studies of this approach are not yet available.[194] Surgical intervention is necessary if perforation appears imminent, as resection of necrotic bowel and/or temporary colostomy can be lifesaving.[49] Elements of treatment of neonatal diarrhea outlined above are appropriate for necrotizing enterocolitis as well. Multiple cases may present in a nursery at one time, suggesting that enteric isolation procedures may be useful in such a circumstance.[60]

Prevention. Although some studies have shown that oral aminoglycoside antibiotics[178] can reduce the frequency of necrotizing enterocolitis, others have not been able to confirm these results,[65] and the cost of such prophylaxis includes the development of resistant strains.[99] Furthermore, absorption of significant amounts of aminoglycosides may occur when these drugs are given orally for the prevention or treatment of necrotizing enterocolitis.[196] More definitive advice about prevention will rest on a better understanding of the cause and pathogenesis of this condition.

Prognosis. Two recent studies of the outcome of 239 infants with necrotizing enterocolitis report survival rates of 45–68% and a significant incidence of intestinal stricture (21%), but an excellent long-term outcome.[246,387]

Skin Infections

The presence of furunculosis, cellulitis, and omphalitis in newborns should be taken very seriously. Although it is common to see a small amount of redness around the umbilicus at the time of cord separation, progressive inflammation despite gentle warm compresses and alcohol cleansing should alert the physician to the possibility of a bacterial infection. Pustules and draining wounds should always suggest that possibility.

Etiology. Vesicles or pustules may be due to herpes or varicella virus, or to acropustulosis,[281] pustular melanosis,[307] or erythema toxicum, benign self-limited skin lesions. Cellulitis and omphalitis may be due to many pathogens, including aerobic bacteria, such as group B Streptococcus, staphylococci, Gardnerella,[268] and anaerobes, including Bacteroides.[68] Remember that Listeria, groups A and B Streptococcus, herpes simplex, and gram-negative bacteria (including Pseudomonas and anaerobes) can all cause the same condition.[206] Some, like Staphylococcus, can progress to bullous impetigo and systemic infection. Others may lead to necrotizing fasciitis.[401]

Diagnosis. In all instances, gram stain and culture of scraped or aspirated material and a blood culture should precede systemic therapy. In some, urine, CSF, and respiratory secretions should also be cultured. Older infants at home should be similarly examined and cultured if fever or other signs suggest systemic infection. It is wise to remember that these signs may be very subtle and nonspecific. Very few infants have had serious complications because of a lumbar puncture or blood culture. More have ended up in tertiary care facilities because of a hesitancy to carry out these procedures.

Treatment. There are few indications for topical antimicrobial therapy in newborns. I know that many practitioners have observed successful outcomes after such treatment. The problem is there is no way to predict which babies are going to develop complications. Since the majority of these localized lesions are due to Staphylococcus or Streptococcus, dicloxacillin 50 mg/kg/day (divided q 12 h in the first week and q 8 h thereafter) should be adequate for a 5–7-day period in most babies. Use of topical antiseptics may also be hazardous, as exemplified by hexachlorophene toxicity, and by hypothyroidism induced by percutaneously absorbed povidone-iodine.[221] Hexachlorophene bathing can be added for patients with proven staphylococcal infections. Progression or persistence of infection should prompt aggressive measures to identify and treat sepsis.

Eye Infections

Conjunctivitis in the newborn should prompt us to consider chlamydia, gonococcus, Staphylococcus, Listeria, group B Streptococcus, *Haemophilus influenzae,*[96] herpes simplex, and silver nitrate among the causes. Conjunctivitis may also be a component of systemic infection. For example, a newborn developed meningococcal meningitis 6 days after the initiation of treatment with topical chloramphenicol and oral ampicillin for purulent conjunctivitis.[213] Since vaginal colonization and infection with *N. meningitidis* have been reported, the patient may have had primary meningococcal conjunctivitis acquired during delivery.[39]

Since the etiologic spectrum of neonatal conjunctivitis is wide, smears and cultures are indicated.[23] The gram stain is invaluable in sorting out the causes of infection. Silver nitrate conjunctivitis is usually noted in the first 3 days of life, and usually resolves with saline rinses, or no therapy, within 24–48 h.[333] Neonatal conjunctivitis should be diagnosed and treated aggressively. This usually means systemic antimicrobial therapy for all except chemical causes (see Chapter 4).

Otitis Media

Otitis media is different in newborns! Approximately 6–40% of acute suppurative otitis media in babies are due to gram-negative bacteria.[53] *Staphylococcus aureus* may also be present more frequently than in older infants and children. *Streptococcus pneumoniae* and *Hemophilus influenzae* are also commonly causative.[397] Nasotracheal intubation for longer than a week predisposes newborns and infants to this infection, as does feeding in the supine position.[52]

The etiologic spectrum is wide. Therefore, consideration of a diagnosis of otitis media in the newborn constitutes an indication for tympanocentesis. Gram stain and culture of the middle ear pus will guide therapy in a specific fashion. In other respects, neonatal otitis media is similar to that seen in older children with nonspecific presenting signs, such as irritability or lethargy, fever, cough, vomiting, diarrhea, tachypnea, and anorexia.[438] Since these signs and neonatal otitis may also be present with sepsis, a complete examination and appropriate cultures are recommended before prescribing therapy.

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4

Upper Respiratory Infections

Respiratory infections are the most common infectious diseases worldwide.[23] My own experience is in North America, where most children acquire between seven and nine respiratory infections per year.[232] In the United States this results in a total of nearly 500 million episodes and 2 million hospitalizations annually. About 8 million hospital days are utilized for treatment of respiratory infection-related disease and over 2 billion dollars are spent yearly to purchase medications for the specific and symptomatic management of these conditions.[215] If you are still not convinced, talk to parents, teachers, or health care providers, or visit the general pediatric clinics or hospital wards during the winter months in temperate climates.

The topic of respiratory infections has been arbitrarily divided into those affecting the upper and the lower tract, depending on the predominant anatomic location of inflammation, whether above or below the larynx, respectively. This is not always appropriate, since laryngitis may be associated with the common cold syndrome (usually classified as an upper respiratory infection) in many children, yet is surely a component of croup and laryngotracheitis in other patients. Nonetheless, the larynx is a convenient anatomic marker for describing clinical syndromes. In general, lower respiratory infections are more prolonged and likely to be associated with systemic toxicity.

Many of the respiratory viruses were discovered in the decades following the 1960s. Hence, it is not surprising that we have acquired only a rudimentary knowledge of the epidemiology, pathogenesis, and scope of many respiratory infections. Our efforts to prevent and treat these infections are even more primitive.

Epidemiology

The peak incidence of viral respiratory infections is found in the second year of life, although the most severe infections, and proportionately more lower respiratory infections, occur in the first year.[75] Boys seem more frequently infected than girls; however, this may reflect expression of clinical illness rather than frequency. Many of these epidemiologic characteristics are derived from studies of middle and lower socioeconomic North American children and their families. Culture, season, epidemics, caretaking habits, size of family, geography, nutrition, and a variety of host factors affect the expression of respiratory infection.

Etiology

The vast majority of respiratory infections of children are caused by viruses, and in many cases concomitant or superimposed mycoplasma or bacterial infections also occur. Some generalizations can be made. The commonest viruses encountered include rhino, parainfluenza 3, adeno 5, and enteroviruses. Epidemics of influenza virus may alter these statistics dramatically in any given year. Similarly, age may make a marked difference. For example, *Mycoplasma pneumoniae* infections are more frequent in school children and adolescents than in children ages 1–5 years. The subject of bacterial infections is considered last, since they represent a small proportion of the total causes of respiratory infection. The most important organisms involved are *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae,* and *Staphylococcus aureus.* Many other bacteria can become important in certain situations. This is illustrated by the prevalence of gram-negative bacterial infections in nosocomial pneumonia, and of opportunists in a wide variety of susceptible hosts. Despite their relative infrequency, bacterial and fungal infections require special attention because of the associated morbidity and the fact that some can be prevented (e.g., pertussis), and many can be effectively treated with specific antimicrobials.

Treatment and Prevention

Treatment or prevention of nonspecific respiratory infections with antibiotics, immunoglobulins, or mixed bacterial vaccines has no scientific basis and is not recommended. Patients with recurrent respiratory infections should be investigated for appropriate predisposing conditions, rather than treated in a nonspecific fashion. The uses of targeted vaccines, therapies, and isolation procedures are addressed below.

Frequent Respiratory Infections

Clues to the presence of underlying immune deficiencies include genetic (family member with demonstrated or possible immune deficiency, parental consanguinity), phenotypic (dwarfism, telangiectasia), microbiologic (repeated fungal, staphylococcal, unusual bacterial infections), and clinical (pneumonias, skin and lymphatic system abscesses, fulminant sepsis, chronic purulent otitis media) characteristics (Chapter 12).

Results of investigating infants with repeated viral upper respiratory infections and recurrent or persistent otitis media (in the absence of purulent drainage, perforation, etc.) are generally unrewarding. Some of these infants may have low serum concentrations of IgG but this usually represents the lower end of physiologic hypogammaglobulinemia. Unless concentrations are below 50 mg/dl, or there are associated laboratory findings (dysgammaglobulinemia, abnormal cell-mediated immunity, neutropenia), treatment with immunoglobulin is not indicated. In fact, such therapy may retard the natural maturation of the antibody-producing system or impede efforts to define conditions that may benefit from specific preventions, therapies, or immunologic reconstitution (Chapter 12). Other host defenses may be responsible as well. For example, in a recent survey of 119 children with recurrent respiratory infection, those with recurrent pneumonias had decreased neutrophil bactericidal capacity while those with repeated upper or lower respiratory infections had reduced neutrophil chemotaxis.[16] Others have reported deficient leukocyte interferon production in such children.[104]

Rhinitis

Let's start at the nose. Many upper respiratory infections begin with an episode of sneezing, nasal congestion, and rhinorrhea. The nose functions as an aerator and plays a role in phonation. It is also the drainage site for sinus secretions and tears. The nasal mucosa is extremely vascular and richly supplied with lymphatic tissue. Inflammation of the nasal passages, therefore, can be associated with abnormalities of respiration, speech, and swallowing and can interfere with adequate drainage of the sinuses and nasolacrimal duct and, if the nasopharynx is involved, eustachian tube. Hence isolated rhinitis is unusual.

Etiology

Some of the causes of nasal inflammation and discharge are listed in Table 4-1. Respiratory viruses are by far the commonest causes of rhinorrhea, and the common cold syndrome the most frequent clinical diagnosis. These infections may also have associated pharyngitis, tonsillitis, anterior cervical lymphadenitis, and tracheobronchitis. Bacterial etiologies are rare at present, although the debate about the importance of pneumococci, Haemophilus, and *Staphylococcus aureus* in colored and purulent nasal discharges continues. The anterior nares are the usual site

TABLE 4-1. Etiology of Rhinitis

- Infection
  - Rhinovirus
  - Coronavirus
  - Parainfluenza
  - Other respiratory viruses
  - *Streptococcus pyogenes*, group A
  - *Corynebacterium diphtheriae*
  - *Treponema pallidum*
  - Other bacteria
- Impetigo
- Sinusitis
- Allergy
  - Seasonal or perennial vasomotor rhinitis
- Foreign body
- Anatomic
  - Septal deviation
  - Cerebrospinal fluid leak
- Drugs
  - Nasal vasoconstrictor
  - Cocaine abuse

for colonization by *Staphylococcus aureus*, and these bacteria are present in approximately 85% of infants and children with or without infection; pneumococci are present in 40% and Haemophilus species in 23%. Thus, interpretation of culture results from this area is very difficult. In addition, there are no controlled studies of antibiotic therapy in the treatment of rhinitis, so that the question of therapy remains unanswered.

One attempt to correlate the characteristics of nasal discharge with bacterial flora gave the following results in 285 patients and 229 controls.[89] Crusting and redness below and around the nares was significantly associated with the presence of group A *Streptococcus pyogenes*. Otherwise, color, thickness, and duration of nasal discharge were unrelated to the nasal bacterial flora. In the absence of definitive studies, it seems prudent to culture the nasal discharge when impetigo-like lesions are seen and to treat those with group A *Streptococcus pyogenes* infections with systemic penicillin for approximately 10 days. Otherwise, nasal discharges should be allowed to resolve spontaneously. In rare instances, diphtheria, syphilis, sinusitis, and intranasal impetigo may be associated with purulent rhinitis. Certainly the presence of rhinitis in newborns, unilateral rhinitis in individuals of all ages, persistent (more than 2 weeks) discharge, and rhinitis in immunodeficient hosts require special consideration. The degree of purulence and the quantity of foul-smelling discharge associated with an impacted piece of wax crayon can be astounding.

The Common Cold Syndrome

School-age children, or infants in homes with school-age children, have approximately six common cold syndromes per year. Most are short-lived with resolution of systemic signs within 2 or 3 days and rhinitis within 7–10 days. Because of the frequency of colds in households with two or three children, parents and physicians sometimes have the impression that rhinorrhea is constant throughout the winter season.

Respiratory viruses usually colonize the upper respiratory tract first. Many, such as rhinovirus, stimulate intense nasal inflammation. Rhinitis is the most prominent feature in most infants and children, although the earliest symptom of illness is often a sore throat (may precede rhinitis by 2–4 days). Malaise, nasal congestion, sneezing, and rhinorrhea quickly follow. Infants may have a 24–72 h duration of fever, but this is less common in older patients. Young infants seem more distressed by nasal congestion, and often have anorexia and difficulty feeding. In contrast, older children often seem rather oblivious to the presence of upper respiratory infection.

Complications. Despite the frequency of the condition and its usual propensity to be short-lived and benign, complications do occasionally occur. These include sinusitis, secondary to swelling of the nasal mucosa and obstruction of sinus drainage, otitis media, and infections of the submucosa and soft tissue spaces of the head and neck.

Allergic Rhinitis

Next to infection, allergies constitute a major cause of persistent nasal discharge. Although there is a tendency toward clear discharge with allergy, and purulence with infection, there is much overlap. Allergy can often be identified by the presence of eosinophils in nasal secretions obtained by blowing the nose or by using a cotton swab to obtain a nasopharyngeal sample.[147] Eosinophils are rarely seen in the presence of viral or bacterial upper respiratory infection. Eosinophilic nonallergic rhinitis, characterized by nasal eosinophilia, negative allergy skins tests, and a normal serum IgE concentration, is benefited by topical or systemic corticosteroid therapy.[187]

Treatment. Specific antimicrobial treatment of rhinitis is limited to group A streptococcal infection, syphilis, or diphtheria. The presence of impetigo, nasal abscesses, otitis media, or sinusitis may also require antibiotics.

Use of nose drops for control of rhinitis is rarely warranted. In young infants who experience difficulty eating and sleeping because of nasal congestion secretions should be aspirated before these activities by means of a soft rubber bulb or some other appropriate gentle suction device. Older children rarely suffer ill effects from rhinitis, although their appearance may be less than tidy. Use of vasoconstrictors may make them look better, but may defeat the purpose, i.e., drainage of secretions from the nasal passages and associated sinuses and ducts. Moreover, the frequent use of nasal vasoconstrictors can lead to rhinitis due to rebound nasal congestion, sometimes called "rhinitis medicamentosa."[22]

Another approach toward the symptomatic therapy of viral rhinitis has been to use systemic decongestants and antihistamines. Although anecdotal reports of efficacy abound among laymen and professionals alike, most controlled studies demonstrate minor or no benefits, and some side effects and expense are to be expected.[47] These medications should rarely be prescribed for infants under 1 year of age, because drying of mucous membranes and toxicities associated with these agents may be pronounced in this age group. Aerosols and room sprays can be especially hazardous.[55]

Prevention. Prevention of viral upper respiratory infections, including the common cold syndrome, depends on personal hygiene and knowledge of the mechanism of spread of the infection.[246] Common cold syndromes due to rhinovirus are generally spread by direct contact.[159] Aerosolization of large droplets is frequent with sneezing and profuse coughing, but these droplets rarely carry more than a foot or so from the infected subject and require deposition directly onto conjunctival or nasal mucous membranes for infection to follow. This can be accomplished by touching contaminated surfaces and subsequent nasal or conjunctival inoculation.[81] Surprisingly, oral ingestion of rhinovirus is much less efficient in causing infection. Thus, avoidance of direct contact by means of handwashing and proper disposal of secretions is the mainstay of prevention.

Parents should be advised to follow these simple procedures and to avoid exposure of high-risk individuals to obviously ill children with common cold syndromes. This is particularly important for newborns and young infants, who tolerate common cold syndromes less well than older children. Patients with underlying pulmonary disease, heart disease, and other systemic conditions may also benefit from these extra precautions. In these individuals, the common cold syndrome is often associated with lower respiratory dysfunction as well.[37] This is exemplified in patients recovering from the pertussis syndrome, in whom acquisition of upper respiratory infections during convalescence often precipitates renewed bouts of cough, wheezing, and tachypnea.

There are no effective vaccines or specific antiviral chemotherapies[172] available at this time for the prevention of common colds or other upper respiratory infections that cause rhinitis. Interferon shows some potential for the prevention of colds but this approach is still experimental.[211] Mixed common cold vaccine preparations prepared from upper respiratory flora are useless.[107] Is vitamin C effective? Rarely has so much publicity been given speculation about a new prevention or treatment. These attest to the importance of both the common cold and the influence of proponents of the vitamin C theory. However, vitamin C has not been proved to be useful for either prevention or therapy of respiratory infections.[146] Those who prescribe large doses of this material should be aware of the potential hazards of this practice.[58]

Pharyngitis/Tonsillitis

An estimated 12 million cases of pharyngitis are seen by health care providers in the United States each year.[160] Many infectious and noninfectious diseases can present this way. Examples include the common cold syndrome, meningococcemia, agranulocytosis, and neoplasms. Drugs can induce sore throat due to mucosal ulcerations or xerostomia. The vast majority of causes, however, are infectious.

Etiology

Respiratory and enteric viruses are the most common causes of sore throat with and without fever. The child with sore throat, fever, and tender anterior cervical lymphadenopathy may have pharyngitis due to group A *Streptococcus pyogenes.* Patchy or membranous exudates, mucosal petechiae, tonsillar swelling, and cough may be present, whereas conjunctivitis, rhinorrhea, and laryngitis are usually absent. If cough is the predominant sign, streptococcal infection is less likely. Herpangina is usually indicative of coxsackievirus, but has also been seen with herpes simplex infection (Fig. 4–1). This syndrome may also be due to respiratory or enteric viruses, Epstein-Barr virus, mycoplasma and, occasionally, other bacteria (Table 4–2).

Streptococcal Pharyngitis

A diffuse scarlet red or follicular rash over the trunk and extremities, strawberry tongue, chills, malaise, and fever indicate either bacteremia or systemic toxemia, the scarlet fever syndrome. Other rashes (except impetigo) usually suggest the presence of viral pharyngitis.

Streptococcal pharyngitis is most frequent during the winter and spring months. Community outbreaks can be severe and require aggressive diagnosis and antibiotic management. Institutional outbreaks are also reported;[59] in both cases, food, carriers, and/or crowding may play roles in the spread of infection.

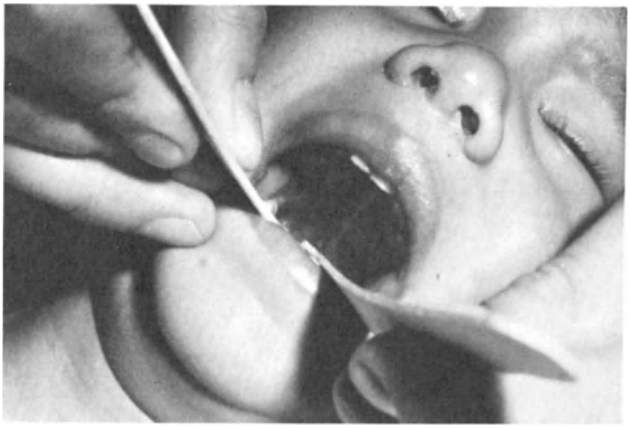

Figure 4–1. Herpangina lesions (white papules on a red base) on posterior palate. For color reproduction of this figure see frontmatter.

TABLE 4–2. Infectious Causes of Pharyngitis/Tonsillitis

- Bacteria
  - *Streptococcus pyogenes* group A
  - *Streptococcus pyogenes* other than group A[143]
  - *Corynebacterium diphtheriae*
  - *Corynebacterium species*
  - *Francisella tularensis*
  - *Neisseria gonorrhoeae*
  - *Neisseria meningitidis*
  - *Branhamella catarrhalis*
  - *Salmonella typhi*
  - Mycobacteria[197]
- Viruses
  - Influenza
  - Adeno
  - Parainfluenza
  - Rhino
  - Herpes simplex
  - Respiratory syncytial
  - Coxsackie
  - ECHO
  - Cytomegalo
  - Epstein-Barr
- Other
  - *Mycoplasma pneumoniae*
  - *Mycoplasma hominis*
  - *Candida albicans*
  - *Chlamydia trachomatis*[254]

Diagnosis

The rationale for diagnosis and management of streptococcal pharyngitis is based on the low (0.4–3%) risk of rheumatic fever during convalescence and the fact that this complication can be prevented by appropriate antibiotic therapy. Additional benefits of an accurate etiologic diagnosis include clues about the cause of scarlatiniform rash, cervical adenopathy, otitis media, peritonsillar abscess, mastoiditis, and glomerulonephritis.

Diagnosis is made by throat culture, but may also be made more rapidly (although somewhat less accurately) by demonstration of group A streptococcal antigen in throat secretions.[158] These simple laboratory procedures should be made available to all patients at modest cost. Admittedly, false-negative and false-positive results are sometimes obtained. The former result from inaccurate swab technique, prior antibiotic administration, and laboratory error, and the latter are due to other β-hemolytic streptococci and the difficulty of differentiating streptococcal carriage from infection. Nevertheless, the benefits of culture far outweigh these drawbacks. They include avoiding antibiotic therapy for one-half to three-quarters of children presenting with pharyngitis, and a more exact knowledge of cause.

Throat Culture Procedure. Throat cultures are obtained by means of a calcium alginate swab rubbed over the posterior pharyngeal wall and the tonsils or tonsillar fossae. The swab is then spread on sheep blood agar (or other appropriate medium), which is incubated for 16–24 h in room air, CO_2, or anaerobically.[121] *Streptococcus pyogenes* group A strains are identified by the presence of β-hemolysis and sensitivity to a 0.04 unit bacitracin disc. Group A streptococci are more specifically identified by immunofluorescence, agglutination, or precipitation by antibody directed against the cell wall carbohydrate. Several other methods are available, including some that speed the procedure by application of the bacitracin disc to the primary isolation plate.[135] Whatever the method, the practitioner would do well to verify its accuracy by periodically obtaining confirmation of positive and negative results from a reference laboratory. One such comparison recently revealed a 25% false-positive rate for a miniaturized office culture test.[126] Controls and quality checks are used daily in hospital-based laboratories and should be part of office diagnostic procedures as well.

Although elevated peripheral white blood cell counts are suggestive of streptococcal infection, use of this criterion or direct examination of smears of pharyngeal exudate are unreliable. Agglutination of antibody-coated latex particles by group A streptococcal carbohydrate in trypsin-treated throat secretions is a promising approach to the rapid diagnosis of streptococcal pharyngitis.[60] To date, throat cultures offer the most optimal basis for treatment and the prevention of suppurative and nonsuppurative complications of streptococcal pharyngitis.[115,160] In certain cases, carriers can be differentiated from those acutely infected, by means of serology, but this approach is seldom practical in clinical practice. In carriers, no significant rise (fourfold or greater) of streptolysin O antibody occurs. Serology and identification of strains by specific antigens (M and T proteins) may be useful in understanding recurrent or persistent infection. In our experience, these cases are most frequently explained by incorrect identification of group A Streptococcus, or by the carrier state with intercurrent viral pharyngitis.[109]

Treatment. Antibiotics should be withheld until culture results are available (this should be a maximum of 48 h in most cases) unless scarlet fever, cellulitis, impetigo, peritonsillar abscess, or some other extrapharyngeal complications of streptococcal infection is present. Empiric treatment before the results of cultures are known is justified in selected circumstances where toxic patients have characteristic signs of streptococcal pharyngitis including palatal petechiae. Such situations may occur during streptococcal epidemics and in households where contacts have a history of rheumatic fever. Therapy should be stopped if cultures do not grow Streptococcus. In most cases rheumatic fever will be prevented even if therapy is delayed up to 9 days after the onset of signs.[115]

If the culture is positive, penicillin is the drug of choice (e.g., phenoxymethyl penicillin 20 mg/kg/day), although cephalexin 50 mg/kg/day, erythromycin estolate 20 mg/kg/day, or erythromycin ethylsuccinate 40 mg/kg/day may also be used. If erythromycin is chosen, however, be aware that 5% of group A streptococci are resistant in certain areas in the United States and up to 72% in Japan.[105] Erythromycin, and possibly other antibiotics, can be administered twice daily without loss of antibacterial efficacy.[51] This may also be true of a 7-day course as compared with the traditionally recommended 10 days, although conflicting results have been noted.[177,210] Perhaps more important than the frequency and duration is compliance. Since most patients will feel better within a few days of initiation of antibiotic therapy, careful verbal and written explanations are useful to enhance the likelihood they will complete the prescribed therapy.[45]

Fever usually lasts 1–3 days, but may not be present at all. Sore throat persists for approximately 5 days. Unless therapy is initiated within the first 48 h of infection, there is little effect of antibiotic therapy on the clinical course of acute streptococcal pharyngitis.

Complications. Progression to suppurative lymphadenitis, scarlet fever, and other bacteremic complications is rare in North America, as is the development of rheumatic fever. For example, the rate for rheumatic fever in the United States is currently estimated at 1.8/100,000 persons annually,[160] with rates as low as 0.5/100,000 in suburban areas.[125] However, in many parts of the world, rheumatic fever continues to be prevalent,[2] and rheumatic carditis remains a dreaded consequence.[248] It is in these latter areas where major efforts are needed to identify infected subjects and ensure compliance with treatment. In many instances this can be done best by intramuscular administration of 1.2 million units of benzathine penicillin. This is rarely needed in North America, where the pain of injection and risk of vascular or nerve injury may approach the risk of rheumatic fever. These injections hurt!

Glomerulonephritis may also result from streptococcal pharyngitis due to particular epidemic strains of groups A and C;[10] however, there is little evidence supporting the efficacy of antibiotics in preventing this complication in individual cases. Of course, detection and accurate treatment of streptococcal pharyngitis and impetigo will reduce the spread of both the acute disease and complications in the community. Efforts to develop effective vaccines for clinical use in the prevention of streptococcal infection have been unsuccessful so far.[15]

Contacts/Followup. Symptomatic family contacts should also be treated, if their throat cultures reveal group A Streptococcus. Followup cultures after treatment and cultures of asymptomatic patients and contacts are not recommended, except where contacts have a history of rheumatic fever. Most individuals still colonized with Streptococcus after appropriate therapy are carriers who create little risk for themselves or their contacts.[108]

Non-Group A Streptococcus Bacterial Infection

What about other treatable causes of pharyngitis? Food-borne outbreaks of pharyngitis have been associated with streptococcal groups C and G infection, and antibody titer rises have also been noted with pharyngitis due to group B organisms.[94] Complications have not been reported and benefits of antibiotic therapy have yet to be demonstrated. This is also true of pharyngitis associated with *Branhamella catarrhalis* and other bacteria that make up part of the normal oral flora. Pharyngitis due to *Neisseria gonorrhoeae,*[241] Corynebacteria,[78] F. tularensis, tularemia,[256] meningococci, and Salmonella requires accurate diagnosis and treatment. Except in rare cases of peritonsillar abscess, *Staphylococcus aureus,* Pseudomonas, and anaerobes are not recognized as causes of pharyngitis that require specific therapy.

Diphtheria

Epidemiology/Pathogenesis

Although rare in developed countries, diphtheria is a potentially fatal infection that should be considered in patients with exudative pharyngotonsillitis. This includes cases of infectious mononucleosis and streptococcal pharyngitis, in which the exudate is confluent and suggests membrane formation. The diagnosis is also likely if such a patient is found to be deficient in immunization, has resided in an endemic area, or has been exposed to diphtheria. The disease is due to *Corynebacterium diphtheriae,* although occasionally other species of Corynebacteria can also cause pharyngitis or other focal infections.[131]

Most of the ill effects associated with diphtheria are secondary to respiratory obstruction and toxin production. Nontoxigenic strains can be converted to toxin producers by bacteriophage. The toxin is an extraordinarily potent inhibitor of protein synthesis, leading to major injury of cardiac muscle and neurologic tissues.[95]

Human carriers of this organism may be either asymptomatic or ill.[225] Sometimes both toxigenic and nontoxigenic types of *C. diphtheriae* are present simultaneously in the respiratory tract. Cutaneous sites may also be colonized and can contribute to the spread of this disease.

Clinical Manifestations. All degrees of illness may be seen. In partially immunized hosts, mild localized pharyngitis may be noted; asymptomatic carriage can also occur. Pharyngeal, ocular, and nasal infections are all possible, with tonsillopharyngeal and laryngeal involvement being most lethal. The disease occurs after a 2–5 day incubation period and the predominant sign is exudative pharyngitis. Some patients rapidly progress to develop a grossly enlarged neck due to cervical adenopathy. A large membrane is formed and respiratory distress may occur without warning.[95] Rarely, *Corynebacterium diphtheriae* and other species may lead to septicemia.[102]

A death rate of approximately 12% has been documented in recent American cases.[52] Neuropathy develops in about 10% of patients and clears spontaneously with appropriate supportive care. Other toxic complications include cardiomyopathy and, occasionally, central nervous system damage. More characteristically, peripheral or cranial nerves are involved, especially cranial nerves IX and X.

Diagnosis. The diagnosis should be suspected in patients with tonsillar and/or pharyngeal membrane formation and in those who are underimmunized and appropriately exposed by residence or contact. There is no time to wait for the results of cultures in this disease! Although fluorescent antibody techniques can be utilized for identification of the organism, reagents are not standardized and not widely available. Thus, the clinician must make a decision without immediate laboratory confirmation. In many respects these patients will resemble those with severe streptococcal pharyngitis, although the membrane is darker and much more adherent to the mucosa than in the latter condition. Gram-stained smears may be suggestive, but are rarely diagnostic (Fig. 4–2).

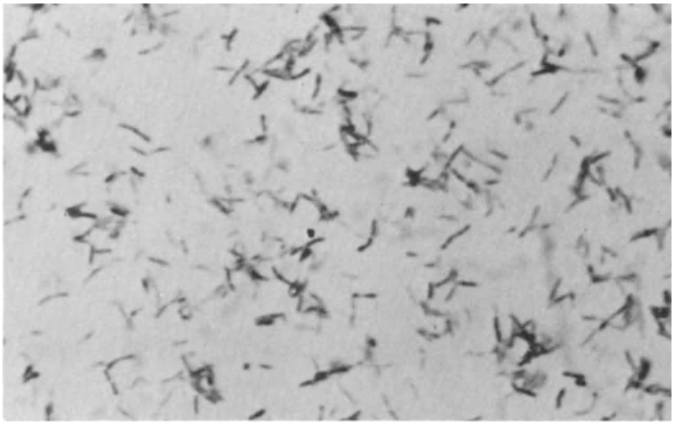

Figure 4–2. Gram-stained smear of *C. diphtheriae*.

Specimens should be obtained before antibiotic therapy and cultured on Loeffler's and tellurite agar. Toxigenicity can subsequently be determined by a gel diffusion method, the Elek test. Rarely, paraquat ingestion[230] and peritonsillar abscess[118] may mimic clinical diphtheria.

Treatment. The first priority in the treatment of diphtheria is maintenance of a patent airway. Laryngoscopy should be performed in almost all patients. If laryngeal diphtheria is present, tracheostomy is usually required.[52] Antitoxin should be administered intravenously, after appropriate skin testing to rule out acute hypersensitivity reactions to horse serum (see Chapter 1). Forty thousand units should be given intravenously to patients with mild disease, and 100,000–200,000 units for those with severe malignant diphtheria.

Penicillin therapy should also be given in order to decrease the number of bacteria and reduce contagiousness. Erythromycin can also be used; however, erythromycin-resistant strains have been described.

Patients who recover from diphtheria should undergo a Schick test, and if the result is still positive, should be appropriately immunized.

Antibiotic and immunization procedures for contacts of patients are also indicated. If susceptible contacts have been intimately exposed to the patient prior to therapy, penicillin should be administered and the patient observed carefully for approximately 5 days. Subsequently, appropriate immunization should be carried out. Eradication of asymptomatic carriage with penicillin or erythromycin, administered for 5 days, is also useful to interrupt outbreaks.[225]

Nonbacterial Causes of Pharyngitis

Viruses are responsible for more sore throats than any other cause. This is a prominent early symptom in the common cold syndrome, influenza, and infectious mononucleosis. The latter is often associated with exudative pharyngitis, also noted occasionally with adenovirus and coxsackievirus infections. Clues to a probable viral etiology are sometimes present in the form of systemic signs (e.g., coryza with rhinovirus, myalgia with influenza, lymphadenopathy with Epstein-Barr virus infections) or local features (e.g., herpangina with coxsackie, gingival, and/or buccal lesions with herpes simplex, or conjunctivitis with adenovirus). These considerations are relevant to explain the cause of certain syndromes (e.g., infectious mononucleosis), and to plan strategies for prevention (e.g., in contacts of influenza A- or herpes simplex-infected patients) and treatment.

Diagnosis of viral pharyngitis is usually made by history and clinical features and, in selected cases, by exclusion of group A streptococcal infection. The two occur together in a minority of patients. Viral and/or mycoplasmal cultures are indicated in certain high-risk hosts or contacts. Examples include children with leukemia, in whom exact knowledge of etiology is often critical to diagnosis and management of febrile episodes.

Rarely, nonstreptococcal oropharyngeal infection in adolescents may lead to anaerobic (predominantly Fusobacterium and Bacteroides) septicemia with septic pulmonary emboli, empyema, and other focal abscesses.[101]

Otitis

Otitis is a term that refers to inflammatory conditions of the external, middle, and inner ear (Table 4–3). Otitis media is probably the most common infectious condition of children. A review of a pediatrician's practice showed that treating otitis media occupied approximately one-

TABLE 4–3. Classification of Otitis

- Otitis externa
  - Acute
  - Chronic
- Otitis media
  - Acute suppurative
  - Chronic suppurative
  - Acute serous
    - "De novo"
    - Postinfectious
  - Chronic serous
- Otitis interna
  - Labyrinthitis

third of his time.[49] Occasionally, as with perforation of the tympanic membrane, otitis media may occur in combination with otitis externa.

Otitis externa: Acute

Acute otitis externa is usually acquired secondary to some insult to the normal integrity of the lining of the external ear canal. Normally the canal is protected by a layer of cerumen, an acid pH, fine hairs, and intact skin.[38] Aggressive removal of wax, scratching of the lining of the canal, or other minor trauma may set the stage for bothersome infections. Highly sensitive nerve endings form part of the protective structures in this area, and as a consequence inflammation becomes especially distressing to the patient. Sometimes the trauma is the result of insect bites, excessive exposure to humidity, water, or overaggressive cleaning of the external ear. In all of these, *Staphylococcus aureus* and *Streptococcus pyogenes* are the most common causes of acute infection. The predisposing insult (e.g., swimming) should be avoided and instillation of topical antibiotics, such as bacitracin, neomycin, or polymyxin will assist in clearing these infections, usually within less than 5 days. A gauze wick may be used for this purpose. Topical corticosteroids may be useful in reducing the local inflammatory response. It is possible that aspirin by mouth may provide similar relief by virtue of its antiinflammatory and analgesic properties.

Otitis externa: Chronic

Otitis externa of longer duration, and with a more pronounced inflammatory response, deserves extra attention. A gram smear and culture are indicated and many practitioners prefer to add a corticosteroid to the topical antibiotic therapy in such instances. History should be directed toward exclusion of less common causes of otitis externa such as herpes simplex, foreign body, or an unusual pathogen.

Profuse discharge from the ear, and the presence of systemic signs, conductive hearing loss, inner ear pain, tinnitus, dizziness, etc., should suggest involvement of the middle and, in some cases, inner ear. In these cases therapy needs to be administered systemically and should be directed against common middle and inner ear pathogens (see below). Needless to say, the patient should avoid introduction of water into the inflamed external canal and should not use any method of mechanical cleansing. Chronic inflamed external canals may develop in patients with underlying dermatologic conditions, such as eczema. In these cases, and in some neglected cases in which a variety of oils, analgesics, and other whimsical remedies have been applied, superinfection with *Pseudomonas aeruginosa*, other gram-negative bacteria, or fungi may occur. Topical polymyxin or colimycin drops applied three or four times daily and before sleep should be prescribed; nystatin should be added if fungi are present.

Chronic cases can require 2–3 weeks of gentle irrigation and topical medication for resolution. Removal of foreign bodies, of course, is critical.

Otitis externa: Invasive (Also Called "Necrotizing" or "Malignant")

The incidence of truly invasive external otitis is extremely low. The majority are due to Pseudomonas (Proteus or Staphylococcus aureus[14] occasionally) and occur in debilitated subjects, mostly with diabetes mellitus.[54] These infections require control of predisposing factors and aggressive antibiotic therapy, usually with ticarcillin and tobramycin. Often surgical debridement is needed.[220]

Otitis Media

Epidemiology. Acute suppurative otitis media is one of the most common and challenging problems facing the primary care practitioner treating children.[238] The condition may present in a nonspecific fashion and the diagnosis may be difficult. Moreover, these infections are frequently recurrent and distressing to patient, family, and physician.[161] Approximately 50% of infants in North America will have one episode of otitis media during their first year of life and 75% by the second year. The prevalence and etiology of otitis media are similar in most countries.[67] The peak incidence of acute suppurative otitis media is between the ages of 6 months and 5 years. Beyond the age of 2 years, otitis media becomes less frequent, although some children experience additional ear infections around school entry at 5 or 6 years of age. This may be associated with renewed exposure to frequent upper respiratory infections.

The clinician making a diagnosis of otitis media in young infants needs to remember the frequency of the condition and its frustrating propensity to recur. There are some analogies to urinary tract infection in young girls. At the time of diagnosis of the first documented instance of both infections, a careful explanation of the pathogenesis, clinical course, and expected recurrences and problems should be discussed with the parents. Forewarned is forearmed! Many of the difficulties of handling otitis media derive from the misconception that some physicians have about the "curability" of this infectious disease. Until we know more about its pathogenesis and the anatomic and physiologic aspects of the host/parasite relationship, there is little likelihood that otitis media can be permanently cured in most situations. With careful management, however, the child can be expected to outgrow the condition by age 2 years in many cases, and by 5 years in almost all. Most serious and permanent complications can be avoided. Physicians and families who do not understand these realities will spend much energy and expense searching for a permanent solution before this time.

Pathogenesis. Some of the factors involved in the pathogenesis of acute suppurative otitis media are outlined in Table 4–4. Several probably interact in most children. The short and straight eustachian tube in the infant may allow entry of nasopharyngeal and oral secretions, food, and flora into the middle ear cavity.[53] It is this possibility, and the oft-noted association of otitis media with feeding in the head-down position, that prompts recommendations to sit the infant up while feeding.[17] This is of particular importance when the infant has a respiratory infection. Other aspects of nutrition seem to play a role as well, since breast-feeding may be protective in high-risk populations, such as Eskimos and Indians in isolated environments. In one survey, the lowest incidence of ear infections occurred in Eskimos breast-fed for more than 1 year.[194] Frequent respiratory infections also contribute to eustachian tube dysfunction through several mechanisms.[191] Similarly, allergy may play a role in older infants and children.[199] The flora characteristically associated with otitis media are ready and waiting in upper respiratory sites in most infants and children.

Genetic factors may play a role in predisposing the host to recurrent otitis media, although this has been difficult to define because of the frequency of the infection in the general population. Certain hosts, such as patients with Down syndrome, and others with congenital anomalies of the facial, palatal, and mandibular bones have more frequent episodes of otitis media as well.

TABLE 4–4. Pathogenesis of Acute Suppurative Otitis Media

- Anatomic
  - Infant eustachian canal less angulated
  - Cleft palate
- Nutrition
  - "Prop feeding"
  - Malnutrition
- Infection
  - Viral upper respiratory infection[90]
  - Bacterial middle ear infection
- Allergy
  - Tissue edema + exudate[119]
- Immune deficiencies
- Foreign body
  - Nasotracheal intubation
  - Indwelling nasogastric feeding tubes
- Environment
  - Cigarette smoke[119]

TABLE 4–5. Etiology of Bacteriologically-Positive Acute Suppurative Otitis Media

Microorganism	*Approximate frequency (%)*
Streptococcus pneumoniae	40
Haemophilus influenzae	20
Streptococcus pyogenes group A	10
Branhamella catarrhalis	10
Combined (usually pneumococcus and *Haemophilus*)	5
Staphylococcus aureus	1

Etiology. The most common bacteria isolated from the middle ear are listed in Table 4–5 according to their relative frequencies.[161] *Branhamella catarrhalis* (formerly named *Neisseria catarrhalis*) seems to play a more prominent role than was formerly appreciated.[221] *Staphylococcus epidermidis, Streptococcus viridans,* respiratory viruses, and mycoplasma are infrequently encountered.[242] In about one-quarter of cases, no specific microorganism is found although polymorphonuclear leukocytes, the characteristic inflammatory cell of acute suppurative otitis media, are present. In the past, bullous myringitis was considered due to *Mycoplasma pneumoniae*; however, careful review of these cases has failed to substantiate this.[183] Another misconception assumed *Haemophilus influenzae* was rarely pathogenic in children over 4 years of age. According to a study of 58 children aged 5–9 years this was shown not to be true—36% had *Haemophilus* in their middle ear exudate.[205] In a small percentage of children (approximately 5%) two common bacterial causes are present concurrently.[169] In patients with viral respiratory infections both virus and bacteria may be present in the middle ear.[111]

The bacteriology of acute otitis media unresponsive to antibiotic therapy includes bacteria resistant to the initial therapy in about 20% of cases.[239] It appears that selection of resistant strains in the upper respiratory tract is one of the prices paid for antibiotic therapy. This has been most clearly shown for ampicillin treatment and subsequent throat colonization with β-lactamase positive *Haemophilus influenzae.*[195]

In the first 2 months of life, gram-negative bacteria, including *E. coli* and *Klebsiella pneumoniae,* become much more common causes of otitis media (see Chapter 3). *Chlamydia trachomatis* is a rare cause.[40]

Diagnosis. It would seem that such a common infection, which occurs behind a "window," should be relatively easy to diagnose. Far from it! This window is well-hidden in the external ear canal, which can be extremely narrow, tortuous, and filled with wax in many infants. This becomes painfully clear to the harried practitioner faced with an irritable, crying, and fearful infant and worried parents. The presentation can be extremely nonspecific, particularly in younger patients. Fever may be absent in up to two-thirds of infants with acute suppurative otitis media, although malaise, anorexia, and irritability are common.[203] The latter symptoms are also frequent with several other diagnoses that may or may not be associated with otitis media. Included among these are pneumonia, meningitis, and a variety of viral syndromes. Many practitioners have had the experience of diagnosing otitis media a day prior to the onset of typical measles rash, roseola infantum, meningitis, or rotavirus gastroenteritis.

What can we do to improve our acumen in making this diagnosis? First of all, remove the wax and debris. Next, do not accept nonspecific symptoms and signs alone. Thus, redness of the tympanic membrane, fever, irritability, and upper respiratory infection are not sufficient for the diagnosis.[161] More reliable signs are bulging of the tympanic membrane, loss of visualization of the ossicles, dullness of the membrane, loss of normal drum mobility with pneumatic otoscopy, and abnormal tympanography.[209] The latter two features of tympanic mobility offer some degree of objectivity in assessing the state of the tympanic membrane and predicting the presence of fluid behind it.[124] Older patients, of course, may report conductive hearing loss, middle ear pain, or pain on movement of the tympanic membrane.

In those cases with equivocal findings, the practitioner may better serve his patient by reexamining him on the following day than by prescribing antibiotics. The complications of otitis media usually occur after the infection has reached a late stage of development. Remember, as many as one-half of the cases of bacterial meningitis we see have received prior antibiotic therapy for suspected otitis media. Although otitis media may, in fact, precede, or coexist with, meningitis, the important point is that these antibiotics have not prevented meningitis in many cases.

When should the practitioner consider tympanocentesis and myringotomy?[30] There is no simple answer to this question; however, certain guidelines are reasonable. In hosts in whom otitis media presents a particular risk and may represent unusual infections, tympanocentesis should be used as part of the initial diagnostic workup. Hence, a tympanocentesis should be performed in newborns, leukemic patients, other immunosuppressed hosts, and patients with coexisting invasive infections. I include meningitis and other bacteremic illnesses in the latter category. This is not only to provide an excellent source for culture, but also to remove a potential focus for recurrent infection. In the rare situation where meningitis is secondary to a contiguous focus emanating from the ear, antrum, or mastoid, the evacuation of pus from the middle ear is an important adjunct to antibiotic therapy.

Tympanocentesis should also be considered in patients with acute suppurative otitis media who have failed to respond to one of the conventional treatments. The vast majority of infants and children will have some relief of the symptoms and signs associated with otitis media within 48 h, if they take a drug appropriate for the infecting organism. If still symptomatic, tympanocentesis may tell why.[239] Tympanocentesis should also be considered in patients who have a recurrence of signs of otitis media within a week or so of completion of the initial course of therapy. In both instances middle ear cultures may reveal resistant bacteria and/or the aspiration may assist in the evacuation of thickened, purulent discharge that can act as a nidus for continued infection.

Myringotomy can be used in place of tympanocentesis, although the specimen is more commonly contaminated with external ear flora when material is collected for culture by this technique. It is better employed for more effective drainage when thickened exudate is discovered in the middle ear and recurrence or therapeutic failure has been noted.[207] The presence of acute suppurative complications or facial palsy is also an indication for myringotomy. Although proposed by some as effective therapy alone for acute suppurative otitis media, myringotomy should rarely be relied upon in modern times as the sole therapy for this condition.[249]

Therapy. There is no one antibiotic, or combination of antibiotics, that will effectively treat all cases of otitis media and none that will cure the condition permanently. The practitioner may choose from several recommended therapies that are directed against the usual causes of otitis media (Table 4-6). Single drugs (amoxicillin, cefaclor[21]) and combinations (trimethoprim/sulfamethoxazole[64] and erythromycin/sulfisoxazole[98]) are effective.[214,223] Special pathogens require more specific selection of antibiotics. The microbiologic information obtained from gram smear and culture will guide the clinician in these cases.

As otitis media is rarely bacteremic and, in the case of Haemophilus, usually due to infection by unencapsulated strains, antigen is not present in the sera or urine of these patients in any great concentrations. This is unfortunate, since knowledge that the infection is due to *Haemophilus influenzae* might suggest more specific therapy. For example, in areas where ampicillin-resistant Haemophilus species exist in high frequency, use of amoxicillin alone would introduce considerable risk of failure. In the absence of knowledge of the exact etiology, therapy directed against *Streptococcus pneumoniae* and *Haemophilus influenzae* is usually initiated. Some features of the commonly prescribed drugs are detailed in Table 4-6. My particular choice is the combination of erythromycin and sulfisoxazole, which has clearly been shown superior to erythromycin alone in the treatment of *Haemophilus influenzae* otitis media. The combination is also effective against ampicillin-resistant strains.[184] A small risk of encountering pneumococci resistant to this combination still exists in approximately 6% of cases. A throat swab to rule out the presence of group A Strep-

TABLE 4–6. Antimicrobials for the Treatment of Acute Suppurative Otitis Media

Drug	*Daily Dose (mg/kg)*	*Cost (US$)*	*Advantage*	*Disadvantage*
Erythromycin/ sulfisoxazole	50/150	8.4	Antibacterial spectrum	Sulfonamide side effects 6% Pneumococcus-resistant
Trimethoprim/ sulfamethoxazole	10/50	6.0	Antibacterial spectrum Palatibility	Sulfonamide side effects Group A Streptococcus resistant 5% Pneumococcus resistant
Amoxicillin	75	10.6	Safety Absorption	Resistant *H. influenzae*
Cyclacillin	100	17.1	Absorption	Resistant *H. influenzae*
Bacampicillin	80	21.9	Absorption	Resistant *H. influenzae*
Cefaclor	40	12.8	Antibacterial spectrum Palatibility	Variable activity vs. *H. influenzae* and *Staphylococcus* Serum sickness-like reactions

tococcus should be performed in patients receiving trimethoprim/sulfamethoxazole, since this drug is less effective against these bacteria. Similarly, the practitioner who prescribes amoxicillin, cyclacillin, or bacampicillin may choose to do a nasopharyngeal culture for ampicillin-resistant *Haemophilus influenzae* type b, since its presence in the nasopharynx may suggest a reason for failure 2 or 3 days after initiation of therapy.[134]

The risks of using penicillin, erythromycin, or sulfonamides alone are substantial. It must be remembered, however, that these risks in most patients refer to the failure to resolve otitis media within a 3- or 4-day period. The disease is often self-limited within 1–2 weeks, even without antibiotic therapy.[249] The latter is not recommended, however, since as many as 20% of these children will have spontaneous perforation of the tympanic membrane without treatment, and as many as 15% can have some of the other complications listed below.

Whatever drug is chosen, adequate dosage and compliance are important. I recommend 75 mg/kg of amoxicillin per day in an attempt to achieve adequate middle ear concentrations of the drug.[112,120] Lower doses may be associated with fewer side effects and lower cost, but possibly at the sacrifice of some therapeutic results. Most of these drugs can be used twice a day as effectively as three times a day.[234]

The duration of antibiotic therapy for otitis media has not been well-studied. It seems reasonably safe to offer the antibiotic for a minimum of 1 week. Equal attention should be given to avoiding intercurrent viral respiratory infections in young infants during the treatment period. Superimposing a new bout of congestive upper respiratory infection on existing eustachian dysfunction and middle ear fluid will often lead to a second bout of otitis media despite antibiotic therapy.

Nasal decongestants have little effect on the frequency, course, or outcome of acute suppuratve otitis media;[157] however, a recent controlled study showed that an antihistamine-decongestant mixture could reduce associated coryza from 9 to 6 days and decrease the likelihood of middle ear effusion at 14 days from 54% to 28%.[149] Whether these effects are worth the risk of adverse reactions (drowsiness, irritability, blurred vision) and extra cost is questionable. Decongestants and antihistamines offer no benefit for patients with otitis media with effusion.[36]

Prognosis/Recurrences and their Management. After 20 or more years of investigation of therapies for acute otitis media, one thing is clear. Failure will be seen in anywhere from 5 to 15% of acute cases and recurrence in more than 50% of infants having their first episode of otitis under 1 year of age.[206] Also clear is the fact that more than half of the patients will persistently have middle ear effusion 10–14 days after the diagnosis of acute otitis media is made,[222] and after appropriate antibiotic compliance.[205] Reexamining asymptomatic patients at this stage provides the practitioner with few guidelines to the ultimate resolution of the acute case or the likelihood of recurrent disease. It may be more informative to reexamine the patient 2–3 months after the acute episode, unless clinical signs suggest that recurrence, continued infection, or other complications have occurred.[50] By 4 months after the diagnosis, middle ear effusion has spontaneously resolved in 94% of infants.[208] This period may be shorter in breast-fed infants.[237] Oral dexamethasone is ineffective in treating these effusions.[137] This time period should be allowed to elapse for almost all children before consideration of more complicated approaches to management. If, during this period, the infant has another episode of otitis media, it is useful to note that approximately one-third of these effusions contain Haemophilus, pneumococcus, Branhamella, or *Staphylococcus epidermidis*.[71] Treatment of these infections and tympanocentesis of failures are useful approaches.

Control of the acute infection, of course, is of the first order. Thereafter the clinician may prefer to use trimethoprim (TMP)/ sulfamethoxazole (SMZ), 4mg TMP/20mg SMZ/kg/day administered at bedtime, to prevent recurrences of otitis media while persistent middle ear effusion is present.[202] Potential complications of this drug therapy, including neutropenia and thrombocytopenia, need to be kept in mind.[8] Decongestants and antihistamines do not appear to reduce the frequency of otitis in these infants.[179] Twice daily sulfisoxazole 75 mg/kg/day,[132] sulfamethoxazole,[201] or bedtime trimethoprim/sulfamethoxazole[77] have been used effectively to reduce the frequency of these bouts of infectious recurrences in infants with or without middle ear effusion and in older children with asthma; pneumococcal vaccine is a useful adjunct to sulfisoxazole in the latter group.[199] Both situations (i.e., persistent middle ear fluid or recurrent otitis) also require careful observation, patient compliance, avoiding respiratory infections, and patience on the part of both the families and physicians. Pneumococcal vaccine may also be useful in preventing recurrences in children over the age of 6 months, but the effect is certainly not dramatic.[139] There is no objective evidence that adenoidectomy will reduce the frequency or severity of recurrent otitis media.[163]

I have gone into some detail about the course, prognosis, and management of patients with persistent middle ear effusion and recurrent otitis media. I suspect that the majority of these infants will outgrow the condition without surgical intervention. Although tympanostomy tubes may appear to solve the problem in some situations, it may not be necessary for many of these patients. Tympanosclerosis (white plaques on the tympanic membrane and nodular deposits in the middle ear submucosa), other risks of surgery, and expense argue against this approach.[161] Although partial conductive hearing loss may be present for a few months with fluid in the middle ear, this has not been shown to produce any long-term sequelae in most instances.[162] Hearing impairment is considered significant if a loss of greater than 20 decibels is measured in a sound-proof room or greater than 25 decibels under other testing conditions. Persistent hearing losses of these magnitudes for longer than 3 months should be treated aggressively to prevent impairment of cognitive, language, and emotional development.[25] Drainage of middle ear fluid and/or tympanostomy tubes may be required.

A more aggressive approach is also suggested by the results of a recent study in which tympanostomy tubes reduced the frequency of otitis media in infants with a prior history of at least three episodes of acute suppurative otitis media.[68] Further experience with this strategy is needed; however, it may be useful in patients who do not respond to medical prophylaxis.

Complications. What is the outcome of otitis media? Acute complications of otitis media are not common, but can be very serious. These include mastoiditis, which may occur in up to 8% of untreated cases of otitis media,[72] facial palsy (suggested by vertigo, nystagmus, tinnitus, hearing loss, and nausea and vomiting), suppurative labyrinthitis, sigmoid sinus thrombophlebitis, brain abscess, and meningitis. Focal cerebritis, extradural and subdural abscesses, and otic hydrocephalus are rarely seen with modern approaches to diagnosis and therapy. When encountered, they usually represent neglected cases of otitis media, use of home remedies, and other misadventures in diagnosis and therapy. The young infant with meningitis may be an exception, however. It is not clear whether the otitis media associated with meningitis is a predisposing factor. The vast majority of cases of meningitis represent bacteremic illness, thought to be an unusual feature of otitis media. The clinician's ability to differentiate isolated otitis media and meningitis from cases in which both exist is understandably limited in young infants. Therefore, lumbar puncture is often required. Failure to respond to appropriate antibiotic therapy after 48 h requires careful reassessment of the patient, including reconsideration of the diagnosis of isolated otitis media.

The vast majority of infants and children outgrow otitis media within 2 years and almost all by 5 years of age.[26] A small number of patients develop chronic otitis media secondary to spontaneous perforation of the tympanic membrane and inadequate drainage. This may also reflect host (e.g., Down syndrome, cleft palate) and nutritional factors, and persistent eustachian tube dysfunction. Most of these patients recover a considerable amount of hearing and middle ear function later in life. Most normal infants and children with single or repeated bouts of acute suppurative otitis media will suffer no permanent complications; however, delay in language development may be frequent in such infants.[66] Rarely, repeated otitis media can be followed by tympanosclerosis, and adhesive otitis media (impaired ossicle movement secondary to mucous membrane thickening) and cholesteatoma can occur. The latter is suggested by persistent otorrhea emanating from a postero-superior perforation.[25]

Chronic Suppurative Otitis Media

Clinical Features. Chronic suppurative otitis media generally occurs after spontaneous perforation of the tympanic membrane in cases of acute otitis media that are diagnosed late, inappropriately treated, or progress due to thickened secretions despite therapy. The patient may present with purulent drainage in the external canal and conductive hearing loss. There are generally few systemic signs and the condition has been present for some time. Underlying the condition are chronic inflammatory changes of the ear, eustachian tube dysfunction, and host factors. For example, middle ear foreign body granulomas, thought to develop secondary to introduction of milk up the short eustachian tube in bottle-fed Eskimo children, seem to predispose them to chronic otitis media.[243] The bacterial flora associated with chronic otitis media often include *Staphylococcus aureus, Pseudomonas aeruginosa,* Haemophilus, and anaerobic bacteria.[29] Rarely, tuberculosis may present as chronic otorrhea,[106] and may be associated with laryngeal and/or pulmonary infection;[5] tuberculous mastoiditis may also be present.[151] The differential diagnosis should also include cholesteatoma, granulation tissue, histiocytosis X, foreign body, tumor, and fungal otitis media.

Treatment. As in acute otitis media, careful removal of cerumen and secretions from the external canal under direct observation is a prerequisite for adequate examination of the external canal and tympanic membrane. A gram stain and culture should be obtained in all cases and systemic antibiotic therapy initiated. As in acute otitis media, this is not the place for topical antibiotics, analgesics, or antiinflammatory drugs.[56] When otitis externa accompanies otitis media, topical applications may be achieved by soaking a gauze wick inserted into the external canal (see Otitis Externa). Risks of instilling drops for pain or antibacterial effects include maceration of the skin of the external canal, obstruction and prevention of adequate examination of the middle ear, and introduction of toxic drugs into the middle ear space with subsequent damage to middle ear structures.[56] Generally, a 4–6-week course of systemic antibiotic therapy and gentle cleansing of the external canal are necessary for recovery from chronic otitis media. Hospitalization may be needed for the initiation of therapy directed against *Pseudomonas aeruginosa.* The future availability of oral drugs active against gram-negative bacteria may obviate the need for hospitalization in many cases. Consultation with otolaryngologists is useful in resistant cases. In some instances, gentle debridement of the external canal and removal of cholesteatoma or other loculated inflammatory material may be necessary for resolution of the condition. Reconstructive tympanoplasty is sometimes required.[224]

Serous Otitis Media

Fluid in the middle ear cavity usually occurs after acute otitis media but may also be present due to obstruction without infection. Some of these cases, which present in the absence of acute suppurative otitis media, may be secondary to allergy.[24] Tympanometry is useful to define the presence of fluid.[153] If no other inflammatory signs are present, the clinician may choose to observe the patient over several weeks rather than institute any specific therapy. Approximately 30% of all such effusions will contain bacteria.*Haemophilus influenzae* is most common in serous fluid and *Staphylococcus epidermidis* in mucoid exudates.[73] If allergic conditions, nasal polyps, or other anatomic obstructions exist, correction of these problems may be the most important aspect of care.

As mentioned above, the presence of serous fluid after acute suppurative otitis media is common and should resolve in almost all cases after 4 months. This fluid may be serous, mucoid, or purulent. Medical management is outlined above. If the fluids persists, myringotomy for the drainage of thickened secretions (sometimes called "glue-ear") and, in rare instances, tube insertions should be considered.[50] Retraction of the tympanic membrane, a variant of chronic serous otitis media, may occur due to persistent or intermittent negative middle ear pressure. Tympanostomy tubes can be used to relieve this condition and restore hearing.

Mastoiditis

Pathogenesis/Etiology

Patients with chronic otitis media and purulent otorrhea are particularly susceptible to mastoiditis.[88] Cholesteatoma may also be present. In most cases, *Staphylococcus aureus, Streptococcus pneumoniae,* and *Streptococcus pyogenes* are the causative organisms in acute mastoiditis,[74] although anaerobes[32] and tuberculosis[136] are also noted in chronic mastoiditis.

Clinical Manifestations. Persistent otorrhea, fever, and irritability should suggest this diagnosis. Earache and headache are often present, as is tenderness localized over the mastoid process. In children under the age of 1 year the pinna is often pushed out and down, whereas those over 1 year more commonly have swelling over the mastoid area.[74] Cranial nerve palsies, particularly of the VIth and VIIth nerves, should suggest the presence of associated venous thrombosis or meningitis.

Diagnosis. The diagnosis of mastoiditis is made by observing the clinical signs described above and radiographs of the mastoid demonstrating the presence of fluid levels or bone destruction. Description of osteomyelitis is enhanced by the use of computerized tomography; however, arteriography may be necessary for complete visualization of venous sinus thrombosis.

Treatment. Antibiotic therapy should be initiated parenterally with high doses of antistaphylococcal and antistreptococcal drugs. Oxacillin 200 mg/kg/day, divided q 6 h, is a reasonable initial choice. Intravenous penicillin should be added in patients with a more chronic course and in those with foul-smelling purulent discharge. Tuberculosis, of course, requires specific diagnosis and management. Of primary importance is the use of surgical drainage in many cases, including those with osteomyelitis and vascular thromboses. In others, myringotomy and antibiotics may suffice.[88]

Complications. Osteomyelitis of the mastoid, venous sinus thrombosis, brain abscess, and meningitis are the most frequent and serious complications of mastoiditis.[250] Fortunately, with early recognition and management of otitis media, mastoiditis is now seen much less commonly.

Sinusitis

The sinuses develop at a variable rate throughout infancy and childhood.[252] Although the maxillary and ethmoid sinuses are present at birth,

TABLE 4-7. Pathogenesis of Sinusitis

- Infection
  - Viral upper respiratory infections
  - Dental abscess
  - Rhinitis
- Allergy
- Polyps
- Foreign body, e.g., nasotracheal intubation[114]
- Adenoidal hypertrophy
- Trauma
- Predisposing conditions
  - Cystic fibrosis
  - Kartagener syndrome
  - Immotile cilia syndrome
  - Hurler syndrome
  - Down syndrome
  - Immunodeficiency
  - Facio-cranial abnormalities
  - Malignancy

they are incompletely formed and are rarely the site of primary infection before the first year of age. One exception is the association of ethmoid sinusitis with orbital cellulitis. The maxillary and frontal sinuses approach adult configuration and location only by the age of approximately 8 years. At this time they can become symptomatic in a more classic fashion. The sphenoid sinus is small and reasonably protected throughout infancy and childhood. Infections of this sinus are unusual in the pediatric population.

Sinuses bear many similarities to the middle ear. They are aerated by short openings into the nasal tract and are lined by ciliated respiratory epithelial cells. These cilia and covering mucus provide the primary defenses for these cavities. The major function is in aeration and, therefore, the amount of fluid they contain is usually minimal.

Pathogenesis

Like the middle ear, sinuses are affected by conditions that affect the normal drainage of mucus and other secretions from these cavities into the nasal passages. Some of these factors are outlined in Table 4-7. They may occur alone or in combination, such as the association of polyps with allergy or cystic fibrosis. Traumatic deviation of the nasal septum may obstruct flow from the maxillary or ethmoid sinuses, thereby leading to infection. Cranial-facial abnormalities include midline facial bone defects, choanal atresia, cleft palate, etc., and may have effects similar to those of allergy, polyps, foreign body, and viral respiratory infection.

Dental abscesses and infections of the nose, skin, and other adjacent structures may lead to sinusitis by direct extension of the infectious process.

Etiology. *Streptococcus pneumoniae, Haemophilus influenzae,* and *Branhamella catarrhalis* are the most common causes of acute sinusitis and maxillary and ethmoid sites are the most common locations (Table 4-8).[253] The sinus fluids of patients with chronic sinusitis contain a mixture of anaerobic and aerobic bacteria.[33] It is conjectural whether all these microorganisms are pathogenic in chronic sinusitis. One possibility is that these abnormal cavities are colonized with respiratory flora after changes in their normal drainage and ciliary functions due to chronic inflammation. Nonetheless, the clinician is wise to include antibiotics active against these bacteria when treating chronic sinusitis.

Children with cystic fibrosis often have maxillary sinusitis on a chronic basis. Examination of the bacteriology of these sinuses have revealed the presence of *Pseudomonas aeruginosa, Haemophilus influenzae,* streptococci, anaerobic bacteria, *E. coli,* and *Staphylococcus aureus.*[217]

In patients with acquired or congenital immunodeficiences a much wider spectrum of etiologic agents may be associated with sinusitis. Examples include mucormycosis in patients with diabetes mellitus, and aspergillus and candidiasis in leukemic patients.[41] A recent report of five children with aspergillosis of the paranasal sinuses emphasizes the roles

TABLE 4-8. Etiology of Sinusitis

Acute
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Branhamella catarrhalis*
- *Streptococcus pyogenes*
- Rhinovirus
- Influenza
- Parainfluenza
- Adenovirus
- Aspergillus

Chronic
- Bacteroides
- Peptostreptococcus
- Peptococcus
- Fusobacterium
- *Streptococcus pyogenes*
- *Staphylococcus aureus*
- *Haemophilus influenzae*
- Fungi[258]

of malignancy, neutropenia and broad-spectrum antibiotics in the pathogenesis of this condition.[20]

Clinical Manifestations. With the exception of ethmoiditis, acute sinusitis usually occurs in children over the age of 5 years and is most commonly associated with facial pain (periorbital or supraorbital), headache, and fever.[252] Younger children may have periorbital swelling and marked systemic toxicity. Purulent nasal discharge, congestion of the upper respiratory tract, otitis media, cough, and foul-smelling breath may also be present.

In advanced cases of sinusitis, swelling of the face adjacent to the involved sinuses may occur over the cheek, frontal area, or orbits. Earlier swelling of the nasal mucosa unilaterally is a clue to the presence of sinusitis, as is the presence of localized tenderness. Retropharyngeal purulent exudate and pharyngitis are less specific clues. Trauma, allergies, and skin conditions can often be differentiated from infectious sinusitis by the lack of systemic signs and the localized nature of the lesion.

Diagnosis. Among the clinical clues mentioned above, local tenderness over the sinus is most important. This is particularly true of older patients and patients with infections of the frontal sinus. The diagnosis of sinusitis should be confirmed radiographically (Fig. 4-3). Useful views include anteroposterior, lateral, and occipitomental. The purpose of these radiographs is to try and demonstrate fluid levels, contiguous osteomyelitis, and asymmetric opacities. Ultrasonography may be useful as well, particularly in differentiating mucosal hypertrophy from fluid.[252]

Definition of etiology is best achieved by needle aspiration. This technique should probably be reserved for situations where initial antibiotic

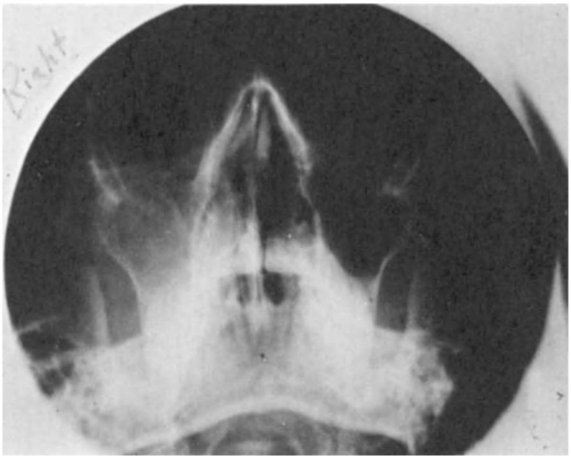

Figure 4-3. Right maxillary sinusitis.

therapy has failed, or in patients who have particularly toxic and/or life-threatening syndromes. Immunosuppresed patients should also be considered for this procedure early, since the etiologic spectrum of sinusitis in these patients is so diverse. In young children general anesthetic or analgesic-sedative mixtures are often needed for this procedure. In others, cocaine can be used for mucosal anesthesia. This should be followed by lidocaine anesthesia of the submucosal area. With a new needle and syringe, the sinus (usually maxillary) should be entered through the inferior meatus (not through the ostium, to avoid trauma to the natural drainage site) and purulent material aspirated as completely as possible. Gram smear and quantitative aerobic and anaerobic cultures should be performed. Although all bacteria isolated may be important, those in concentrations greater than 10^4 cfu/ml (10,000 colony forming units) may be causing most harm.

Blood cultures should be obtained from all patients with systemic toxicity and after needle aspiration, since bacteria may be liberated into the bloodstream by the procedure. Culture of any ipsilateral nasal discharge may also be useful. The interpretation of these culture results must be made cautiously, however. Finding group A *Streptococcus pyogenes* or type b *Haemophilus influenzae* should be taken seriously, as should the finding of aspergillus or zygomyces in immunosuppressed patients. There is less concordance between nasal flora and sinus bacteriology when other organisms are found.

Treatment. Initiation of therapy for acute sinusitis in normal hosts can be made on clinical and radiographic grounds (Table 4-9). Amoxicillin 50–75 mg/kg/day is useful initial therapy for acute sinusitis. Other forms of ampicillin, such as bacampicillin, can also be used.[228] Erythromycin/

TABLE 4-9. Treatment of Sinusitis

Acute
- Amoxicillin 50–75 mg/kg/day divided q 8 h
  or
- Erythromycin/sulfisoxazole 40–100 mg/kg/day divided q 8 h

Chronic[a]
- Amoxicillin 50–75 mg/kg/day divided q 8 h
  or
- Phenoxymethyl penicillin 50,000 mg/kg/day divided q 6 h
  or
- Tetracycline 30 mg/kg/day divided q 6 h

[a] Dicloxacillin 50 mg/kg/day divided q 6 h should be used if penicillinase-producing staphylococci are considered causative. However, this should not be considered adequate therapy for anaerobes. Penicillin, clindamycin, or metronidazole should be added in the latter cases.

sulfonamide or trimethoprim/sulfamethoxazole combinations are useful alternatives.[84] The latter is not consistently active against *Streptococcus pyogenes*; penicillin should be substituted in such cases.

The treatment of complicated acute sinusitis depends on definition of the underlying cause or predisposing condition. If it is obstruction, this should be removed. This is relatively easy for foreign bodies or polyps, but may be more difficult in the face of allergy or congenital abnormality of the facial bones. Decongestants and antihistamines may be useful in allergic conditions, although the risk of drying secretions and reducing drainage needs to be kept in mind. Progression of acute sinusitis despite seemingly appropriate antibiotic therapy is an indication for more aggressive diagnosis and drainage in selected cases.

The mainstay of treatment for chronic and fungal sinusitis is surgical drainage.[258] Penicillin, amoxicillin, tetracyclines, or other antibiotics are adjunctive to drainage and the correction of predisposing conditions. For example, drainage of a contiguous dental abscess may be critical to recovery of associated sinusitis. When abscesses are present, *Staphylococcus aureus* becomes a more prominent cause of sinusitis.

The duration of treatment for acute sinusitis is arbitrary. This depends on the extent of infection at the time of diagnosis and the response to therapy. A minimum of 1 week is useful, although up to 2 weeks may be required. Guidelines include systemic and local findings as well as bacteriologic response, when available. Chronic sinusitis requires therapy for 2–3 weeks in most cases. Therapy needs to be prolonged when osteomyelitis and/or tuberculosis is present.

Complications. These are rarely associated with sinusitis in children but can be extremely serious, in consideration of the locale of these sinuses. For example, the frontal sinus is extremely close to cerebral structures.[181] Hence complications include orbital cellulitis, extradural and subdural empyema, meningitis, and brain abscess. Cortical thrombophlebitis and infarction may present as seizures, focal neurologic signs, or other manifestations of intracranial inflammation or infection.[34] The young patient with sinusitis and systemic toxicity deserves special consideration because of the potential for these complications and the frequency of associated bacteremia. Thus a lumbar puncture may be indicated in young infants with acute ethmoiditis and associated orbital cellulitis.

Infections in and Around the Eye

Periocular infections and sinusitis may be related. For example, ethmoid sinusitis may be followed by periorbital and/or orbital cellulitis. Allergy, foreign bodies, trauma, and surgery may also play roles in the pathogenesis of these infections. Redness and swelling are the most common signs of eye and orbit infections. When acute in onset the causes are often infectious (Table 4–10). When swelling has been present for a week or longer, tumors, fungal infections, tuberculosis,[219] and metabolic causes need to be considered. Bilateral periorbital edema may also be present in patients with allergy, trichinosis, infectious mononucleosis, mucocutaneous lymph node syndrome, leptospirosis, anasarca, congestive heart failure, and the syndrome of inappropriate antidiuretic hormone secretion.

Although sty (hordeolum), chalazion (usually staphylococcal infection of lid sebaceous gland), and lacrimal duct infections may occasionally require systemic antibiotics and drainage, the majority of these conditions are self-limited, with spontaneous drainage frequent after warm compresses (which are also very soothing).[236] Periorbital and orbital cellulitis are discussed in detail below.

Eye infections in infants and children are frequent, and predominantly of a benign self-limited and localized nature. When infection clearly involves the cornea, the interior of the eye, or the orbital tissues, consultation with a specialist in ophthalmology is urgently required. The diagnosis and management of patients with keratitis, iridocyclitis, and endophthalmitis is complicated by the need for careful assessment of corneal injury, visual acuity, and the frequent requirement for intraocular cultures, drainage and, occasionally, direct intraocular instillation of antimicrobial therapy. Conjunctivitis in the newborn is discussed in Chapter 3.

TABLE 4–10. Causes of Acute Periorbital Swelling

Infectious	*Usual Cause*
Sty (hordeolum)/chalazion	Staphylococcal infection of hair follicle/sebaceous gland on eyelid
Conjunctivitis	See text
Dacrocystitis/dacroadenitis	Staphylococcal infection of lacrimal duct/gland
Periorbital/orbital cellulitis	See text
Noninfectious causes	
Trauma	
Allergy	
Insect bite	

Periorbital Cellulitis

Infections in and around the optic orbit are often grouped under the heading of periorbital cellulitis. Primary infections of orbital tissues are quite rare and are usually associated with ocular pathology. More commonly, infections of the periorbital tissues are secondary to sinusitis, adjacent skin infections, or septicemia.[236]

Periorbital tissues are separated from the orbital contents by the periorbital septum, which is a continuation of the periosteum of the frontal and facial bones. The lid is actually divided into anterior and posterior compartments by this layer of fibrous tissue.

One of the most useful ways of discussing these infections has been described by Shapiro et al.[218] Periorbital infections are classified as follows:

1. Infections associated with paranasal sinusitis (Fig. 4–4). These are usually seen in young children with developing ethmoid and maxillary sinuses and recurrent respiratory infections. These patients usually have active sinusitis, which can be documented radiologically, profuse rhinorrhea, and other signs of upper respiratory infection. There is swelling and inflammation of the periorbital tissues and systemic signs are frequent. Nontypable *Haemophilus influenzae* and *Streptococcus pneumoniae* are often causative and the patients are generally between the ages of 18 months and 4 years. Unlike orbital cellulitis, there is no proptosis, ophthalmoplegia, or prolonged morbidity. Treatment is directed against the above bacteria, usually by use of amoxicillin, or by combinations of erythromycin-sulfisoxazole or trimethoprim-sulfamethoxazole. Generally, these medications can be administered orally and clinical improvement is apparent within 2–3 days. A total

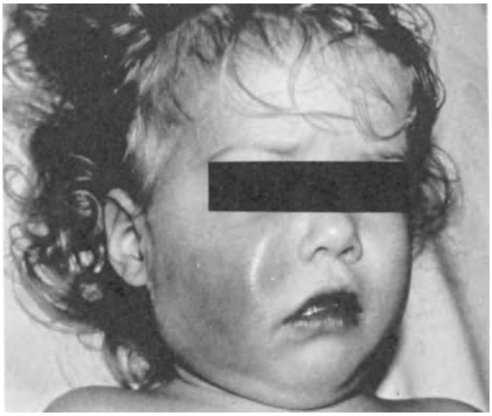

Figure 4–4. Cellulitis secondary to maxillary sinusitis.

duration of therapy of approximately a week is needed unless sinusitis is persistent and requires drainage.[236]

2. Periorbital cellulitis secondary to skin infections. This is easy to diagnose because of the presence of an insect bite, chickenpox lesions, or impetigo on the face, and associated swelling around the eye. In some circumstances (such as insect bite) part of the swelling can be attributed to allergy. Group A *Streptococcus pyogenes* or *Staphylococcus aureus* strains are causative in many of these;[69] however, *H. influenzae* has also been reported.[93] Aspiration of the cellulitis at the advancing border with a 25-gauge needle and a small amount of nonbacteriostatic saline will provide sufficient material for gram stain and culture in most cases. Cultures of the associated skin lesion are also useful. Although blood culture is recommended, it is generally positive only in cases with advanced infection and toxicity. It is useful to document the presence of bacteremia, since it may guide the physician to look for coexistent or subsequent infections. Therapy should be directed against the etiologic agent. If the etiology is unknown, dicloxacillin, or other antibiotics effective against *Staphylococcus* and *Streptococcus* (e.g., cephalexin in a child allergic to penicillin), is recommended. Complications are rare with this type of infection.
3. Periorbital cellulitis secondary to bacteremia (Fig. 4–5). This is a more common condition seen in infants in the first 3 years of life. These infections are generally due to *Haemophilus influenzae* type b[227] and, occasionally, to *Streptococcus pneumoniae,* and are associated with bacteremia in most cases. In some, it is unclear whether the pathogenesis is related to sinus infection (especially ethmoid sinusitis) and spread to the local tissues, or secondary to the bacteremia. Occasionally these patients have associated meningitis, pneumonia, septic arthritis, or other manifestations of bacteremic *Haemophilus* or pneumococcal dis-

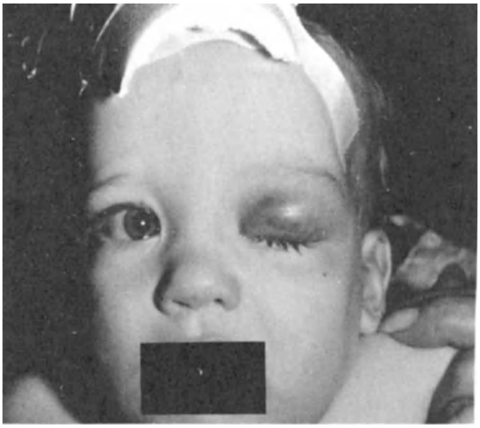
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Figure 4–5. Periorbital cellulitis due to *Haemophilus influenzae* type b.

ease, and one should search for these. Aspiration of the local skin lesions, blood culture, and search for pneumococcal and *Haemophilus* antigens in the serum and urine are warranted. Search for β-lactamase-positive *Haemophilus influenzae* the ipsilateral naris, conjunctival secretions, and respiratory tract is also useful as a guide to therapy. The presence of this type of organism should suggest the need for continuing antibiotics effective against β-lactamase-producing organisms for the entire course of therapy. As with the other conditions, a positive blood culture should prompt a search for other infectious foci and should be repeated to ensure adequacy of antimicrobial therapy. It is useful to obtain a swab from the prepared skin area, as is done for other percutaneous needle aspirations, in an effort to assist in interpretation of the culture results. Often specific therapy may be guided initially by gram stain of purulent conjunctival fluid, nasal discharge, aspirate from the infected periorbital tissues, and/or antigen detected in urine or serum. Approximately 1 week of appropriate antibiotic therapy is effective in most cases.

4. Orbital cellulitis. Fortunately, this is the rarest of the periocular infections encountered, although it is the most serious. This is because the orbital contents are extremely close to the cavernous sinus and because subperiosteal abscess, orbital abscess, and optic nerve inflammation and compression are potential complications. The presence of orbital abscesses can be detected by the use of computerized axial tomography[76] and, occasionally, by ultrasonography.

   Clinical signs that suggest the presence of orbital cellulitis include proptosis, ophthalmoplegia, and decreased visual acuity. These infections are more commonly seen in school-age children and in teenagers, and are often related to penetrating ocular injury, foreign body, or advanced contiguous frontal or maxillary sinusitis. The cooperative older patient may report exquisite pain upon compression of the eye and decreased visual acuity or diplopia. These are extremely serious infections, and are often due to *Staphylococcus aureus*, although a variety of gram-negative and gram-positive bacteria have been reported. Penetrating injuries, with or without a foreign body, may also be associated with fungal infections. Aggressive diagnostic procedures are often needed to establish the presence of an abscess; and drainage is usually effective.

   Antibiotic therapy should be guided by the results of gram stain and cultures obtained from collections of pus. Since vital structures are at high risk, there should be no hesitation to perform needle aspiration, sinus drainage, blood cultures, etc. Initial therapy should include administration of antistaphylococcal antibiotics. If sinus infection is possible, add drugs active against Haemophilus and pneumococcus. Useful combinations are oxacillin and ampicillin, or oxacillin and chloramphenicol. Single drugs, pending culture results, could include cefoxitin, cefuroxime, or ceftriaxone.

Thus the child with a swollen eyelid and red, painful periorbital tissues may represent a diverse spectrum of etiologies and pathogeneses. Diagnosis and management of conditions associated with respiratory infections and sinusitis may be different from those associated with skin infections and those seen with penetrating orbital trauma. It is useful to consider the anatomic and pathogenic events carefully in these patients so that sinus disease, orbital abscesses, dental infections, and systemic complications are not overlooked.

Conjunctivitis

Epidemiology/Etiology

Inflammation may be localized to the conjunctiva, or conjunctivitis may be a component of a systemic infection (Table 4–11). Most recently, a pandemic of enteroviral conjunctivitis has involved an estimated 80 million people worldwide since 1969.[251] The expression of infection has ranged from simple conjunctivitis, lasting 3–5 days, to more serious hemorrhagic conjunctivitis associated with a "polio-like" neurologic syndrome. The etiologic agent, enterovirus 70, has been isolated from patients in widespread outbreaks in India[251] and in Florida.[165] For unknown reasons, neurologic manifestations were common in India, whereas the infections in Florida manifested most frequently as acute hemorrhagic conjunctivitis.

Localized conjunctivitis is caused by both infectious and noninfectious conditions (Table 4–12). Most cases of enteroviral conjunctivitis are seen in the warm summer months, whereas adenovirus is more frequently seen in the fall and winter seasons.[80] Exceptions are not uncommon, however, as illustrated by an outbreak of adenovirus conjunctivitis related to con-

TABLE 4–11. Systemic Conditions Associated with Conjunctivitis

Measles
Leptospirosis
Mucocutaneous lymph node syndrome
Reiter syndrome
Erythema multiforme
Listeriosis
Meningococcal infection

TABLE 4–12. Etiology of Conjunctivitis

- Infections
  - Virus
    - Adenovirus
    - Enterovirus
    - Herpes simplex
    - Varicella zoster
  - Bacteria
    - Haemophilus
    - Staphylococcus
    - Streptococcus
    - *Branhamella catarrhalis*
    - Moraxella
    - Pseudomonas
    - Aeromonas[226]
    - Enteric bacilli
    - *Neisseria meningitidis*[261]
    - Anaerobes
  - Chlamydia
  - Mycoplasma
- *Phthirus pubis* (lice)[3]
- Allergy
- Foreign body
- Ultraviolet light[185]

taminated swimming pool water.[48] Adenovirus is especially communicable and may also present with a variety of associated respiratory conditions. Herpes simplex is an uncommon, but dreaded, cause.

Bacterial causes of conjunctivitis are also frequent, with *Staphylococcus aureus, Haemophilus influenzae,* and *S. pneumoniae* among the most common agents isolated from infected eyes (Fig. 4–6). Occasionally, *Branhamella catarrhalis,* another normal upper respiratory flora, is pathogenic when present in high concentrations in conjunctival fluid.[182] Gonococcal conjunctivitis usually suggests child abuse or use of bizarre folk remedies.[4] Anaerobes are more commonly isolated from infected eyes, although it is unclear whether these bacteria are primarily responsible for the conjunctivitis or are secondary invaders subsequent to viral or mechanical injury.[170]

Clinical Manifestations. Conjunctivitis usually occurs without systemic signs. There is a sudden onset of increased tearing, discharge, pain, photophobia, and conjunctival hyperemia. Itching, palpebral edema, and subconjunctival hemorrhage may also be present. This condition is often bilateral and, in the case of enterovirus, rarely lasts longer than 5 days, although adenovirus[171] and bacterial conjunctivitis may take 1–2 weeks to resolve, even with specific therapy.

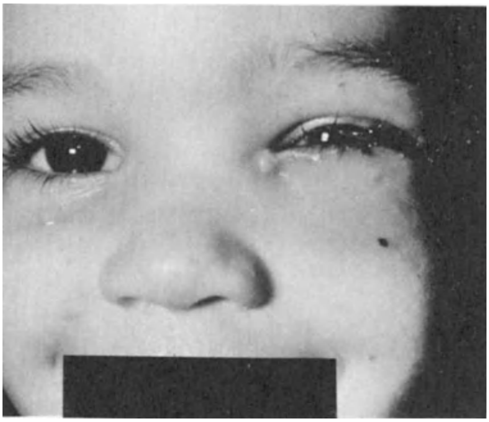


Figure 4–6. Conjunctivitis and periorbital cellulitis due to *Streptococcus pneumoniae.*

Patients, or their parents, often complain of "sticky" eyelids upon awakening in the morning and of some loss of visual acuity.[12] Visual acuity should be checked in all patients with conjunctivitis in whom this is possible. When acuity is decreased, consultation with an ophthalmologist is important to evaluate the possibility of coexistent keratitis. The presence of corneal infection or inflammation may modify therapeutic strategies so that higher concentrations of topical antibiotics and topical corticosteroids may be needed. Moreover, consideration of herpes simplex keratitis is very important in such cases.

Adenovirus Conjunctivitis

The presence of pharyngitis, lymphadenopathy, systemic fever, and conjunctivitis should suggest the possibility of adenovirus as a causative agent. Pneumonia may also be present. It should be remembered that one member of the family may have hemorrhagic conjunctivitis, as a manifestation of adenovirus infection, while a young infant contact may have pneumonia. Rarely, these patients also have gastrointestinal symptoms. Although highly unlikely, the potential for life-threatening infection should be appreciated, as illustrated by death due to disseminated adenovirus type 4 in a 5-year old child who presented with croup and conjunctivitis.[63]

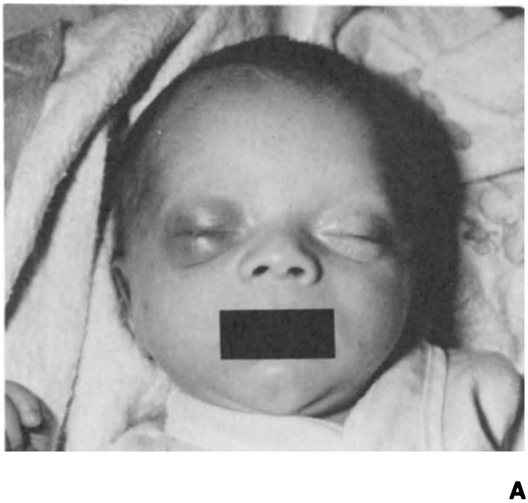
The Conjunctivitis-Otitis Syndrome

The association of otitis media, purulent/rhinorrhea, and conjunctivitis in children in the first 5 years of life suggests that the patient has the conjunctivitis-otitis syndrome.[27] This is most commonly due to *Haemophilus influenzae,* with 55/75 cultures obtained in such patients yielding this organism. Often these are type b, although nontypable Haemophilus organisms are also responsible. These patients are generally febrile, anorectic, and unhappy.

Diagnosis. Epidemiologic and exposure history, and physical findings, will often suggest the specific etiology, knowledge of which dictates the therapeutic approach. In some cases, viral cultures are useful in defining the cause of an outbreak of conjunctivitis. For example, enterovirus 70 is often isolated within 3 days, with the use of human embryonic fibroblast cells.[87] Herpes simplex cytopathic effect is often evident within 1–2 days as well. Bacterial cultures are more useful in other cases. How does the clinician choose? Aside from the historical and clinical features outlined above, microscopic examination of the conjunctival exudate is rapid and informative.[229] Wright stains are useful. The presence of eosinophils in the conjunctival discharge is most compatible with an allergic reaction, whereas polymorphonuclear leukocytes point to a bacterial etiology.[12] Mononuclear cells, inclusion bodies, and giant cells are most commonly seen with viral causes of conjunctivitis. Neutrophils and inclusion bodies in the conjunctival exudate of young infants with conjunctivitis suggest chlamydial infection (Fig. 4–7). Fungi or parasites may also be seen. This simple, relatively inexpensive test is often overlooked, but can be critical in guiding the clinician toward the appropriate diagnostic tests and management. Bacterial, viral, mycoplasmal, chlamydial, or fungal cultures, and/or serology may also be indicated. Periocular inflammation, proptosis, and systemic illness should prompt further examinations.

Treatment. When conjunctivitis is presumed to be bacterial in etiology, topical therapy is often useful (Table 4–13). Drops need to be instilled frequently (every 2–4 h during waking hours). Ointment is preferable in children, since it can be applied less frequently, although some transient blurring of vision occurs. Several topical preparations can be chosen; however, when possible, these should be different from those used systemically. Hence, combinations using bacitracin, polymyxin, gramicidin, neomycin, etc. are preferred to those incorporating drugs that may be used systemically, such as chloramphenicol, trimethoprim, gentamicin, tobramycin, etc. This is true even though some of these combinations (e.g., trimethoprim plus polymyxin B),[70] and single drugs (e.g., gentamicin or tobramycin) are effective.[122] Topical uses of systemic antibiotics may favor the emergence of resistant strains of bacteria and hypersensitization of the host.

Patients with the conjunctivitis-otitis syndrome, and those with meningococcal or gonococcal conjunctivitis, are best treated with systemic antibiotics. Therapeutic concentrations of systemic antibiotics, such as penicillin or erythromycin, are easily achieved in conjunctival discharge, obviating the need for topical treatments (much to the relief of many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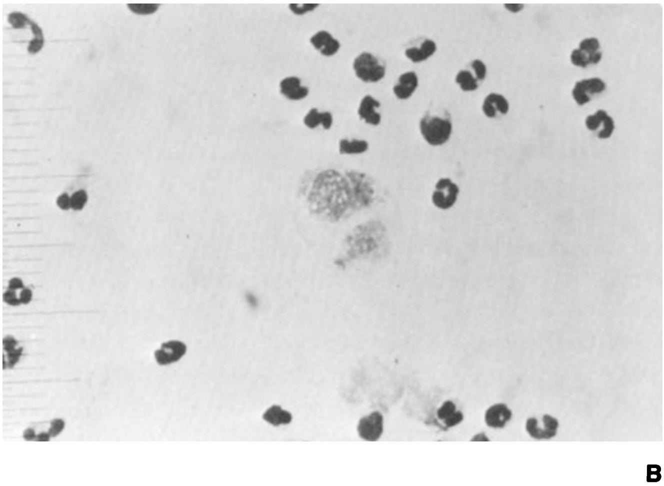

Figure 4–7. Blepharitis and conjunctivitis due to *Chlamydia trachomatis* suggested by the presence of inclusion bodies and neutrophils (and the absence of bacteria) in giemsa-stained conjunctival exudate.

parents with prior experience at trying to get drops or ointment into their children's eyes).

The patient with conjunctivitis should be followed closely since, despite the evaluations mentioned above, some cases of herpes simplex keratitis, chlamydial infection, foreign body, and allergic reactions are missed in the early stages. The patient with bacterial or common viral causes of conjunctivitis is expected to show improvement within 3–4 days in most cases. Occasionally, systemic infection may follow conjunctivitis, as illustrated by the development of meningitis in a 7-month old, 3 days after the diagnosis and topical treatment of culture-positive meningococcal conjunctivitis.[155]

Spread to household contacts is common for some of the viral causes (e.g., adenovirus, enterovirus) and should also be looked for. Common

TABLE 4–13. Topical Antimicrobial Therapy of Conjunctivitis

Drug	*Concentration (Ointment/Suspension)*	*Comments*
Sodium sulfacetamide	10%, 30%	May cause burning sensation.
Erythromycin	1%	May cause burning sensation.
Tetracycline	1%	May cause burning sensation.
Trimethoprim/polymyxin B	1 mg/10,000 units	Gonococcus may be resistant.
Bacitracin/polymyxin B	500 units/10,000 units	May cause burning sensation.
Chloramphenicol	1%	Aplastic anemia is a rare side effect.
Tobramycin	3%	
Gentamicin	3%	

source outbreaks should also be considered, as ophthalmologic instruments have been shown to spread infection in certain situations. Patients with conjunctivitis should be isolated in the hospital, since nosocomial outbreaks may be devastating, particularly when infection is acquired by immunocompromised patients.[129] The clinical manifestations in such spread may be quite variable. For example, three separate syndromes due to adenovirus 19 (conjunctivitis, keratoconjunctivitis, and pertussis-like illness) were noted in a hospital outbreak.[86] Public health approaches recognize that most outbreaks are seen in poor socioeconomic populations with crowding, poor hygiene, and inadequate sanitation facilities.

Chlamydia Conjunctivitis

There are two major types of conjunctivitis due to *Chlamydia trachomatis.* The first, trachoma, is most prevalent, with an estimated 500 million people affected.[49] Of these, 5–10 million are partially or totally blind. This infection is spread from person to person with the eye as the major reservoir. The second form of chlamydial eye infection is inclusion conjunctivitis, which is a milder, self-limited condition acquired from genital reservoirs of *C. trachomatis.*[193]

Clinical Manifestations

Trachoma is a chronic follicular conjunctivitis that can progress to involve both lids and bulbar conjunctiva. Conjunctival scarring and spread of infection is enhanced by abrasions caused by misdirected lash hair growth.

The condition is most prevalent in rural communities in the Middle East, Africa, Asia, and Southern and Central America; however, indigenous cases have been reported in England and Denmark.[150] Both adults and children are affected; however, blindness is more commonly seen in older patients. Poor hygienic and socioeconomic conditions plague these same populations.

Inclusion conjunctivitis is most commonly seen in newborns in developed countries who are born to mothers with genital colonization with *C. trachomatis.* After an incubation period of approximately 5–7 days, approximately half of the infants born to these mothers develop a marked conjunctivitis with redness, swelling, and a profuse watery or mucopurulent discharge. There is often lid swelling as well. From 10 to 20% of these infants may also have an associated respiratory infection.[83] Occasionally, sexually active adults with *C. trachomatis* genital infection may also have inclusion conjunctivitis. These patients have many of the features described for newborns but also may complain of a foreign body sensation and photophobia. Rarely, inclusion conjunctivitis can be due to feline keratoconjunctivitis agent, a member of the *Chlamydia psittaci* group that may be carried by domestic cats.

Diagnosis

The diagnosis of chlamydial conjunctivitis depends on historical and geographic features as well as clinical findings mentioned above. Both trachoma and neonatal inclusion conjunctivitis can be diagnosed by demonstration of chlamydial inclusion bodies in epithelial cells obtained from the palpebral conjunctiva. Iodine or giemsa stain can be used; some success with immunofluorescent staining has also been reported.[189] Confirmation is obtained by isolation of Chlamydia in cycloheximide-treated McCoy cells or other appropriate tissue culture cells. Serologic evidence of infection is provided most reliably by demonstrating a fourfold rise in titer of chlamydial complement-fixing antibody, or, more specifically, by use of type-specific immunofluorescent antibody tests. In both types of conjunctivitis, examination of contacts (ocular for trachoma, and genital for inclusion conjunctivitis) is recommended.

Treatment

C. trachomatis organisms are sensitive to tetracyclines, erythromycin, and rifampin. Sulfonamides are less active against *C. trachomatis* and *C. psittaci* are resistant. Chloramphenicol is ineffective.[57] Topical therapy with tetracycline or erythromycin eye ointment applied three times daily for 5 weeks is used for trachoma. Systemic treatment with erythromycin or tetracycline for 2 weeks is also useful. Improvements in hygienic practices, handwashing, and control of insect vectors and inanimate objects capable of spreading infection should also be considered.

Inclusion conjunctivitis generally requires systemic treatment with erythromycin for a period of approximately 3 weeks. Although symptomatic improvement usually occurs within the first week, nasopharyngeal shedding of organisms may continue and topical or shorter courses of systemic therapy may be associated with relapse or continued contagiousness of the infected individual.[164]

Prevention

If Chlamydia genital colonization or infection is diagnosed during pregnancy, a 2-week course of erythromycin (250 mg orally four times daily) will eliminate *C. trachomatis* from the genital tract and prevent neonatal infection.[83] Silver nitrate drops are ineffective in preventing chlamydial conjunctivitis, and tetracycline ophthalmic ointment may also be unreliable. Erythromycin ointment seems to offer the best prophylaxis against ocular chlamydial infection. Isolation procedures in hospital should include precautions in handling secretions and careful disinfection of any equipment that may have direct contact with the eye, lacrimal fluid, or discharge.

Prognosis

Chlamydial conjunctivitis can be prevented by improved hygienic practices and reduction in sexually transmitted genital infections. Early diagnosis and treatment can obviate scarring and complications in almost all cases. Unfortunately, this is not easy to do where large numbers of affected individuals are located in rural areas or in inner-city populations, receiving little health care. In such circumstances, chronic conjunctivitis, conjunctival scarring, and, occasionally, corneal scarring may supervene. Generally speaking, neonatal and adult inclusion conjunctivitis are milder conditions. Nutritional factors, hypersensitivity due to reinfections, and superinfections may play roles in the different clinical outcomes of these conditions. Nevertheless, trachoma is a preventable cause of blindness and deserves careful attention.

Herpes Simplex Eye Infections

Clinical Features

Herpes simplex type 1 is the commonest cause of herpetic ocular infections beyond the newborn period; however, type 2 infection is common in infants and can be seen at any age. The disease in newborns is characteristically more virulent than at other ages and is usually part of a systemic herpes infection. As such, infection of all ocular tissues is not uncommon, and keratitis and retinitis often coexist in these patients, along with central nervous system and cutaneous infection.[43] Occasionally, older infants may also have ocular involvement with systemic infections, particularly herpes encephalitis. An example is an 8-month-old with fatal encephalitis and herpes simplex chorioretinitis.[44]

Beyond infancy, herpes eye infections are most commonly expressed as keratitis or keratoconjunctivitis. The initial infection is often asymptomatic; hence, recurrent keratitis is most frequently encountered in clinical practice. Primary infection may have associated skin vesicular lesions and conjunctivitis. In the absence of skin lesions and uveitis, the difficulty of differentiating herpes simplex from other causes of conjunctivitis is great, and probably accounts for many primary infections of a self-limited nature. The great risk to the patient, however, is recurrent infection, which varies in extent from small punctate lesions of the cornea to branching filamentous (dendritic), or larger coalescent (geographic keratitis), ulcerations. These recurrences are seen in the presence of circulating antibody, and progressive scarring with subsequent loss of visual acuity is the major complication. Patients are usually well with recurrent disease, although they may have systemic manifestations with primary infection. These include fever, malaise, and, occasionally, preauricular lymphadenopathy.

Diagnosis

How can the clinician differentiate herpetic keratitis from other causes of keratitis and conjunctivitis? This is a difficult task, since examination of the eye in young infants and children is not easy.[173] Clinical clues, however, include the presence of a mononuclear cellular response in the lacrimal discharge of a patient with conjunctivitis. If giant cells or intranuclear inclusion bodies are seen, this is also helpful. When vesicular skin lesions coexist, or the history suggests contact with a patient with herpes, or there is a lack of response to seemingly appropriate antibiotic therapy, viral cultures will be extremely helpful.

Management

The natural course of herpetic keratitis in children is not well-studied, but it is assumed that, as in adults, the frequency of recurrences and the degree of stromal and corneal damage are directly related to scarring and loss of vision. Ophthalmologic consultation is imperative.

Ocular herpetic infection in the newborn period or in an immunocompromised patient[97] is an indication for systemic antiviral chemotherapy. Acyclovir or vidarabine can be used (Chapter 2). Primary herpetic keratitis beyond the newborn period should probably also be treated in this way, as well as with topical antivirals. However, the latter is more easily said than done, since the application of ointment or drops every few hours in the eyes of infants and young children is not easy.

Debridement of scar tissue and corneal lesions, as well as topical antiviral therapy, are the mainstays of treatment for primary and recurrent disease. Three percent acyclovir is as effective as 3% vidarabine when used as an ointment applied every 2–3 h during waking hours.[166] Two percent trifluorothymidine (trifluridine) is equivalent to 3% acyclovir as well;[123] however, interferon may enhance the effect of topical antiviral chemotherapy.[46] Healing time for recurrent lesions is usually around 4 days and the frequency of recurrence is unpredictable. Children have the added disadvantage of amblyopia as a potential risk associated with decreased unilateral visual acuity.

The primary care health provider's role in this disease is suspicion of the diagnosis in its earliest stages. Although conjunctivitis is often considered a minor infectious disease, it is a disaster in a small number of patients who turn out to have a primary herpetic infection.

Other Causes of Keratitis

Isolated infections of the cornea are rare in infants and children. Herpes simplex infection accounts for most of these. Other rare causes include Shigella,[196a] diphtheria,[39] Azotobacter,[130] and a variety of invasive infections secondary to surgery or trauma. Wearers of soft contact lenses may develop keratitis due to a variety of pathogens including Pseudomonas.[257] Keratomycosis (fungal keratitis) is occasionally encountered after ocular trauma or secondary to foreign bodies. Amphotericin B therapy is usually required, although recent experience with oral ketoconazole is promising.[103]

Endophthalmitis

Pathogenesis/Etiology

Endophthalmitis refers to infections of internal structures of the eye. The condition is generally acquired in two ways: (1) postsurgical or posttraumatic; in these cases *Staphylococcus aureus* and a variety of gram-negative bacteria and opportunists[85] are most frequently causative; (2) indigenous or metastatic infection; this is seen after bacteremia or fungemia. Bacterial causes can include pneumococcus, meningococcus,[141] and *Streptococcus pyogenes*, as well as *Haemophilus influenzae* in patients with associated bacteremia and meningitis.[235] Opportunists, such as *Bacillus cereus*, may be causative in intravenous drug abusers.[216]

Fungal causes are diverse and are most frequently seen in severely immunocompromised patients, and in those with extensive burns, or those who are receiving broad-spectrum antibiotics or parenteral alimentation therapy. Candida endophthalmitis is most frequent.[231] However, any opportunists may cause severe ocular damage in this type of patient, as illustrated by infection due to Petriellidium, a soil contaminant ordinarily of low virulence.[144]

Toxocara canis is also an important cause of chronic endophthalmitis and retinal granuloma.[18]

Clinical Manifestations/Diagnosis

The condition should be suspected in a patient who develops a red, swollen, painful eye, in association with the above predisposing conditions. Moreover, this complication may occur after ocular surgery or trauma and should be suspected in all bacteremic and fungemic patients. The consequences are grave and may include loss of vision and diffuse panophthalmitis with subsequent loss of the eye. Abscesses and inflammation of other orbital tissues can be differentiated from eye globe infection by computerized tomography and ultrasound techniques. Hypopyon, or pus in the anterior chamber, is most often a sign of bacterial infection, but occasionally may be due to leukemic infiltrate.[96] Specific therapy must be individualized and depends on accurate etiologic diagnosis. Hence aspirations of vitreous or aqueous fluid are essential. These should be examined by conventional smear and culture techniques. Occasionally, as in suspected toxocariasis, antibody determinations in these fluids may be useful.

Treatment

Surgical consultation is recommended. Antimicrobial therapy initially is directed against the common causes of infection, depending on the pathogenesis, as outlined above. Although a variety of antimicrobials enter aqueous secretions when this chamber is inflamed, intraocular injections and, occasionally, vitrectomy[85] may be necessary. For example, cefoxitin can reach concentrations in the anterior chamber in excess of 6 μg/ml.[110] However, drainage of pus from this site may be more important than the actual antibiotic concentrations. Other antimicrobials enter ocular compartments less well. This is particularly true of amphotericin B, which has been injected into the vitreous for the treatment of Candida endophthalmitis.[231] Local tissue concentrations may be prolonged after such injections, so that repeated doses may not always be necessary. Other successful approaches to the therapy of Candida endophthalmitis include combinations of intravenous amphotericin B with rifampin[133] or 5-fluorocytosine.[9]

Topical and systemic prednisone are often effective in controlling inflammation due to Toxocara endophthalmitis, but vitrectomy may be needed in some cases.[18]

TABLE 4-14. Infectious Causes of Chorioretinitis

Congenital
  - Cytomegalovirus
  - Toxoplasmosis
  - Herpes simplex virus
  - Rubella
  - Syphilis

Acquired
  - Toxocariasis
  - Candidiasis
  - Histoplasmosis
  - Syphilis (late secondary or tertiary)
  - Tuberculosis
  - Aspergillosis
  - Amebiasis
  - Brucellosis
  - Onchocerciasis
  - Cysticercosis (*Taenia solium*)
  - Cytomegalovirus[174] infection
  - Herpes simplex infection
  - Toxoplasmosis (most are probably reactivation of congenital infection)

Chorioretinitis

Many infections can involve the choroid and retina (Table 4-14). Most of the classic causes of congenital infection may result in newborn chorioretinitis, but a much broader differential diagnosis is possible in older children and adolescents. Cytomegalovirus chorioretinitis is most commonly seen in congenitally infected newborns, but can also be acquired in both immunologically compromised and competent hosts.[61] Sarcoidosis, retinoblastoma, and traumatic causes should also be considered.

Toxoplasmosis is the most frequent cause of chorioretinitis beyond the newborn period and may present as fulminant infection.[188] Although most cases represent reactivation of congenital infection,[79] several family outbreaks also support a role for acquired infection.[7] Serologic titers are usually unchanged; however, a sensitive technique has been developed to detect intraocular IgG toxoplasma antibody, which may be helpful in the diagnosis of this condition.[247] Treatment consists of administration of pyrimethamine, sulfadiazine, and steroids for 2–3 months in most cases. Trisulfapyrimidines and clindamycin have also been recommended.[196] Severe visual impairment may result after several recurrences.

Soft Tissue Infections: Head and Neck

Infections of the subcutaneous and submucosal spaces of the head and neck, mostly in the form of cellulitis or abscess, have the potential for grave complications. The spaces are usually defined by fascial planes. In the midline they include retropharyngeal, prevertebral (between the retropharyngeal space and the body of the cervical vertebrae), sublingual, and submental spaces.[198] Those in the lateral direction include peritonsillar, lateral pharyngeal, and submandibular spaces. Facial and buccal cellulitis is discussed in Chapter 7.

Pathogenesis and Etiology

Most of these infections follow trauma or focal infections of the oral cavity. These include tonsillitis, pharyngitis, dental abscess, gingivitis, stomatitis, and combinations of these. Dental extraction may not necessarily lead to local abscess, but may provide the entry site for oropharyngeal flora into the submucosal tissues.[42] The resultant infection is usually consistent with cellulitis in its early stages, and abscess later on.

The microbes causing these infections are primarily derived from the normal flora of the oral and upper respiratory tracts. For example, 90% of the gingival flora are anaerobic bacteria, including Bacteroides, Fusobacterium, and anaerobic staphylococci and streptococci. Aerobes include *Streptococcus viridans, Branhamella catarrhalis,* and, in a considerable number of children, *Streptococcus pneumoniae,* nontypable *Haemophilus influenzae,* and *Staphylococcus aureus.* These flora are affected by age, nutrition, dentition, hygiene, hospitalization, and antimicrobials. These deep tissue infections, therefore, often contain several different species of bacteria, including aerobes and anaerobes. Those involving dental trauma or peridontal infection more commonly include anaerobes, whereas those involving the nasopharynx and tonsils more commonly include *Streptococcus pyogenes,* Staphylococcus, *Streptococcus pneumoniae,* Haemophilus, and anaerobes.[31,65] Rarely, Actinomyces, Clostridium, Lactobacillus, Veillonella, and Eubacterium are present in these lesions.

Clinical Manifestations

Several distinct syndromes are described, although there is much overlap. In certain areas, such as the submandibular spaces, these infections are often referred to as "Ludwig's angina." In others, the terms peritonsillar or peripharyngeal abscess may be used. I prefer using the anatomic location and the characteristics of the infection to describe the condition, e.g., submental cellulitis or abscess.

These patients are usually in some distress, with considerable pain on swallowing, tongue movement, speaking, etc., depending on the localization of the infection. Upper airway obstruction may also occur.[142] In advanced stages, signs include swelling, superficial and deep tenderness, drooling, and a "bull neck" appearance. Drooling is more commonly seen in young infants. Physical examination may reveal swelling around the tonsils or sublingually. This may be obvious upon external examination of the neck as well. Retropharyngeal and prevertebral infections are more difficult to delineate, and may require digital palpation. Occasionally this must be done with the patient anesthesized.

Diagnosis

Clues to be obtained from the history include a previous history of dental extraction (particularly molars), dental abscesses, oral trauma, or pharyngotonsillitis. Physical signs have been described above. Sometimes patients may also have meningismus or torticollis. A lateral radiograph of the neck is useful in defining some of these infections, particularly those in which the retropharyngeal space is enlarged. Particular attention to the distance between the cervical vertebral body and the pharynx should be made.[142] Sometimes, a barium swallow may assist this evaluation. Radionuclide taken up by inflammatory cells, such as gallium-67, may also be useful in localizing these infections.

Oropharyngeal cultures may be useful, particularly in soft tissue infections secondary to pharyngitis, tonsillitis, and focal infections of the oral cavity. In other cases, gram stain and culture of material obtained by percutaneous needle aspiration of the lesion, or at incision and drainage, are important. A blood culture should be taken after needle aspiration or incision. Antibiotics may be started immediately after these cultures are obtained.

Differential Diagnosis

In the retropharyngeal space, cystic hygromas, hemangiomas, and primary neurogenic tumors need to be considered, although these swellings are present for a longer period of time and are not usually associated with local and systemic inflammation.[142] Midline and anterior masses include thyroid lesions and hypoglossal cyst; located more laterally are bronchogenic cysts, thyroid tumors, and neoplasms.

Treatment

Depending on the severity of the case, the patient may require intravenous hydration, maintenance of an adequate airway, and analgesics. Most of these patients require hospitalization. Antibiotic therapy effective against *Staphylococcus aureus* and other aerobes and anaerobes of the upper respiratory tract should be initiated immediately after acquiring appropriate cultures. As an example, oxacillin and ampicillin or oxacillin and penicillin can be administered intravenously. Cephalosporins such as cefoxitin can be used in patients who are allergic to penicillins. Lesions that have already formed abscesses, those associated with complications (see below), and those that are impinging upon vital structures require drainage.[138] General anesthesia is usually required in children. Bilateral tonsillectomy is indicated with a second episode of peritonsillar abscess, or with severe recurrent tonsillitis, despite adequate antibiotics and surgical drainage of the initial peritonsillar abscess. As many as 50% of children may require this approach.[91]

Antibiotic therapy can be adjusted to a more narrow spectrum as soon as culture results become available. In many cases the oral route is satisfactory, with appropriate monitoring. Patients with adequately drained lesions may require shorter durations of therapy (5–10 days), whereas those who are treated without surgery should usually undergo antibiotic therapy for 10–15 days. These decisions need to be individualized, depending on the infecting microorganism, the site, host characteristics, and clinical and microbiologic responses.

Complications

If one considers the anatomy of these spaces, it is not surprising that rare, but life-threatening, complications can ensue. Examples include septic thrombophlebitis of the internal jugular vein and *Fusobacterium necrophorum* septicemia,[213] and carotid artery erosion with infections of the lateral pharyngeal spaces. These compartments are also traversed by the sympathetic chain and cranial nerves IX, X, XI, and XII. Suppurative mediastinitis and pleuropulmonary,[156] intracranial, and hematogenous[186] spread have all been observed, as have ruptures into the trachea and esophagus and respiratory obstruction.

Epiglottitis

Consideration of the diagnosis of acute epiglottitis demands prompt action because the major complication of this infection is acute respiratory obstruction. Approximately 80% of cases are seen in children between the ages of 1 and 5 years, but can occur at any age. It is most prevalent in the winter months, although cases occur in the summer as well.

Etiology and Pathogenesis

Haemophilus influenzae type b is the major cause of epiglottitis. The disease is associated with bacteremia in almost all cases, although it is unclear whether colonization and infection of the epiglottis precedes or follows the bacteremia. Occasionally, respiratory viruses and other bacteria, such as group A or C Streptococcus,[200] have been implicated.

Clinical Manifestations

Epiglottitis is characterized by an abrupt onset of fever and toxicity, associated with sore throat and some pain on swallowing.[13] Occasionally, uvulitis is also present.[180] The voice is often muffled and the patient may refuse to move his head and neck, although Kernig's sign is absent. The disease progresses rapidly over the first 24–36 h to include respiratory distress, noisy inspiration, flaring of the nostrils, chest wall retractions, and dysphagia. The respiratory rate and pulse are increased initially, but may be decreased later on due to the need for additional inspiratory effort. In the most seriously involved cases, the child assumes a still, sitting-up position, leans forward, and breathes with an open mouth. Such posturing and drooling are critical signs suggesting a markedly impaired respiratory status.[13]

Diagnosis

The diagnosis of epiglottitis should be based on clinical criteria. Laboratory tests should not be relied upon to suggest the diagnosis, even though a negative serum C-reactive protein may point to croup as an alternate diagnosis.[168] In fact, venipuncture, aggressive examination of the throat and epiglottis, lumbar puncture, and throat swabs may be sufficiently traumatic to trigger acute respiratory obstruction in such a patient. Depending on the status of each patient, an adequate airway should be maintained and humidified oxygen supplied before and during transport to an intensive care facility.

A lateral neck X-ray is a relatively noninvasive test useful for confirming the diagnosis, but should precede definitive management only in patients without advanced signs of respiratory embarassment. The patient should be accompanied by personnel and resuscitation equipment. After the airway is established, and the child otherwise stabilized, a blood culture can be obtained and the serum and urine can be examined for the presence of Haemophilus antigen. If the patient is intubated, the epiglottis should be cultured. Swabs of the throat and epiglottis before intubation are not recommended.

In approximately 25% of cases of epiglottitis, pneumonia and/or cervical lymphadenitis are also present.[148] Meningitis is seen in a small number of such patients as well. Lumbar puncture should be reserved for patients with persistent meningeal signs after the establishment of an adequate airway.

Treatment

The most important and life-saving treatment consists of adequate oxygenation. The patient should be left in the upright position as much as possible. Although observation in an intensive care setting is useful in experienced hands, early intubation or tracheostomy is safest. The least morbidity is associated with humidified oxygen administered via nasotracheal tube.[62] In centers where tracheostomy is more readily available, this procedure is safest. Nasotracheal intubation is preferred since the mean duration of intubation is rarely longer than 3 days. Fiberoptic laryngoscopy may be a useful guide to tracheal extubation.[154]

Antibiotics should be added as soon as possible, but should not take priority over respiratory and cardiovascular support. Ampicillin, 200 mg/kg, and chloramphenicol, 75 mg/kg/day, should be given in 4 divided doses. Moxalactam, cefoperazone, ceftriaxone, and several other cephalosporins active against *Haemophilus influenzae* can also be used. The route of therapy depends on the patient's illness. Parenteral antibiotics are rarely required for more than 2 or 3 days. A total duration of 7 days is adequate in almost all cases. Prolongation of antibiotic therapy is indicated in cases with slow sterilization of the blood. When this occurs, associated pneumonia, lymphadenitis, empyema, or meningitis should be suspected.[148]

Prognosis

At present, mortality from acute epiglottis is seen in approximately 2% of cases. This is usually due to fulminant disease and/or late diagnosis, difficulties in transportation, or other misadventures in diagnosis and management. Death is almost universally due to respiratory obstruction. Recurrence is extremely unusual and has been reported by one author to occur only once in 500 cases.[13]

The prevention of invasive Haemophilus infections in family or day-care center contacts is similar to that described for Haemophilus meningitis (see Chapter 9).

Cervical Lymphadenitis

Cervical lymphadenitis is considered here because of the frequent involvement of anterior and posterior cervical lymph nodes in soft tissue infections of the head and neck, and in upper respiratory infections. Remember, postauricular and occipital nodes are commonly palpable in the absence of disease in infancy but rare after 2 years of age, whereas submandibular and cervical nodes are rarely palpable in infants but commonly in children.[11] Inflammation of the lymph nodes in the sublingual, submental, and periauricular areas is also common. The etiologic spectrum is large and may reflect pathology in the skin, subcutaneous tissue, sinuses, eyes, and oral cavity.

Epidemiology

Swelling of the lymph nodes in the head and neck is unusual in newborns. *Staphylococcus aureus,* group B Streptococcus, and gram-negative bacteremia may be responsible, as may unusual flora of newborns such as *Mycoplasma hominis.*[175] Neoplastic disease and congenital cysts should be considered in the differential diagnosis of lymphadenopathy in this age group.

Acute lymphadenitis of school-age children is most commonly associated with upper respiratory infections, such as streptococcal pharyngitis, tonsillitis, herpangina, and herpes simplex stomatitis, or may occur without evidence of associated infection. Thus, it is not surprising that cervical lymphadenitis is more commonly seen in winter months, when respiratory illnesses are more prevalent.

Pathogenesis

Knowledge of the anatomic area drained by particular nodes facilitates the search for the underlying cause.[262] For example, submental lymphadenitis is most commonly associated with infections of the lower front teeth or floor of the mouth, whereas occipital lymphadenitis is usually associated with inflammatory conditions of the scalp. Sublingual nodes drain the tongue and posterior aspects of the lower teeth, and cervical nodes the posterior pharynx and adjacent portions of the neck. Preauricular nodes are associated with inflammation of the parotid glands and the external auditory canal. A careful search of the drainage area will often reveal the primary inoculation papule in tularemia or cat-scratch disease, or may define the *tinea capitis,* seborrhea, or tick associated with occipital lymphadenitis. It is presumed that the genesis of the majority of cases of isolated cervical lymphadenitis is in oropharyngeal colonization (often with an inflammatory or traumatic lesion that has completely healed by the time lymphadenopathy is noted).

Etiology

It is helpful to think of the causes of lymphadenitis of the head and neck in terms of the duration of the swelling, epidemiology, and the presence of associated pathology. Examples of the latter include impetigo, pediculosis capitis, and conjunctivitis.

The duration of illness may offer other clues to the diagnosis (Table

TABLE 4-15. Causes of Lymphadenitis: Head and Neck

- Acute (1 week or less)
  - Primary
    - *Staphylococcus aureus* infections
    - *Streptococcus pyogenes* group A infections
    - Other bacterial infections
  - Secondary to:
    - Pharyngitis
    - Tonsillitis
    - Dental abscess
    - Stomatitis
    - Soft tissue infections
    - Skin infections
- Subacute (1–4 weeks)
  - Epstein-Barr virus infections
  - Tularemia
  - Cytomegalovirus infections
  - Toxoplasmosis
  - Visceral larva migrans (toxocariasis)
- Chronic (longer than 4 weeks)
  - Atypical mycobacterial infections
  - Tuberculosis
  - Histoplasmosis
  - Cat-scratch disease
  - Neoplasms/histiocytosis
  - Sarcoid
  - African trypanosomiasis

4-15). Epidemiologic factors of importance include exposure to tuberculosis; ingestion of raw milk; travel; exposure to wild animals, ticks, and cats; and outbreaks of histoplasmosis, or streptococcal infections. The vast majority of cases of lymphadenitis in the anterior cervical chain are due to common bacterial pathogens.[260] Hence, approximately one-third of cases are due to *Staphylococcus aureus,* one-third to group A *Streptococcus pyogenes,* and one-third to a variety of pathogens.[11] This differential diagnosis grows as the lymph nodes remain persistently enlarged.[212] Tuberculous lymphadenitis is still common in endemic countries,[176] whereas atypical mycobacteria is a more frequent cause of granulomatous cervical adenitis in children in a North America.[190]

Clinical Manifestations

Basic to discussion of lymphadenitis are clinical definitions of normal and abnormal lymph nodes. Since many normal lymph nodes are palpable, criteria for pathology are often subjective. Factors involved include the age of the patient (palpable lymph nodes greater than a few millimeters in size are rarely seen in newborns and young infants), frequency of upper respiratory infections (school-age children with repeated bouts of tonsillitis may have persistently enlarged anterior cervical lymph nodes without any pathology other than reactive hyperplasia[192], or repeated skin infections (nonspecific lymphadenopathies are commonly seen with impetiginized skin lesions, furunculosis, etc.) and features of the physical examination (local signs of inflammation, size, fluctuance, consistency, and mobility). In addition to size, other markers of pathology include tenderness, stony hard consistency, fluctuation, matting, or the presence of sinuses or dimples. For example, fluctuation without marked systemic signs suggests cat-scratch disease and, occasionally, staphylococcal infection. The presence of draining sinuses suggests actinomycosis, tuberculosis, atypical mycobacteria, or fungi as causes (Fig. 4-8).

Acute lymphadenitis may be associated with fever, malaise, dysphagia, and local tenderness. These usually improve within a few days after the initiation of appropriate therapy or are self-limited within a week in the majority of cases due to acute viral infection. Persistent lymphadenopathy generally falls into one of two categories. One encompasses associated systemic signs, such as weight loss, persistent fever, and anemia or neutropenia. These signs should prompt early consideration of biopsy. That is because the likelihood of lymphoma, sarcoma, and other neoplasia is enhanced in these patients.[113] More commonly, systemic signs are minimal or absent and the patient has persistent swelling, with or without pain.

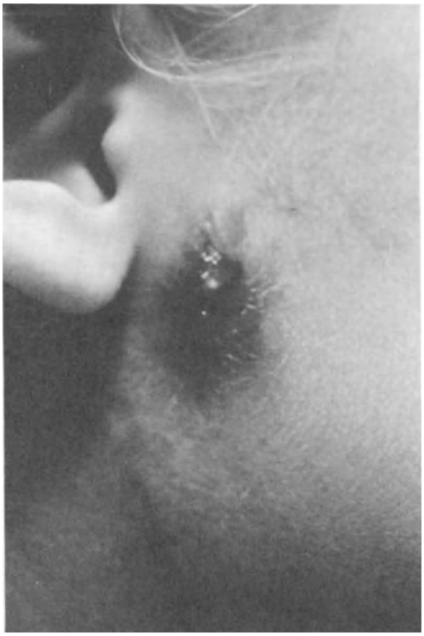

Figure 4-8. Preauricular lymphadenitis with draining sinus characteristic of atypical mycobacteria infection.

Diagnosis

The approach to the diagnosis of lymphadenitis of the head and neck in the infant or child depends on many of the factors outlined above. Acute anterior cervical lymphadenitis is commonly due to streptococcal pharyngitis, or to other inflammatory lesions of the mouth and throat, and these are relatively easy to diagnose. When this occurs without other localizing findings, etiologic diagnosis may be aided by needle aspiration of the node, although this is usually unnecessary in the normal host. That is because the etiologic differential diagnosis is reasonably narrow and a clinical response is expected in the majority of cases after a short course of therapy directed against *Staphylococcus aureus* and *Streptococcus pyogenes.* Of course, the diagnostic workup should include a detailed history about tuberculosis, exposure to wild animals, ingestion of raw milk, travel, and systemic signs that would suggest a more serious condition. In most cases, the clinician need proceed no further. Baseline measurements of the node should be taken and a therapeutic antibiotic trial embarked upon.

When the host is abnormal or the patient has failed to respond to therapy directed at the common causes of acute cervical lymphadenitis within 4–5 days, a more aggressive diagnostic workup is justified (Fig. 4-9). In particular, this includes newborns, immunocompromised hosts, those with supraclavicular and/or matted or hard lymph nodes, and patients with systemic signs. Evaluation should include a reassessment of the history and physical findings, including careful examination of the teeth and mouth, search for papules and ticks, history of tuberculosis and travel, and repeated measurement of the lymph nodes. At this point, it is useful to rule out anemia and leukemia by obtaining a complete blood count and smear. A Mantoux skin test should also be applied. If the skin test is negative (less than 5 mm induration and/or erythema at 48 h), aspiration of the node can be performed. The skin should be prepared with alcohol and povidone-iodine. The prepared area should be cultured in order to define the presence of Staphylococcus or other skin contaminants. Then an 18- or 21-gauge needle containing a small amount (0.1 ml) of nonbacteriostatic saline can be inserted through the skin. The aspirated material should be gram-stained and cultured appropriately.

If tuberculosis or atypical mycobacterial disease is suspected, excisional biopsy is preferred to needle aspiration or incision, since the latter are often associated with poor healing, sinus drainage, and recurrence.[244] Specific skin tests for the diagnosis of atypical mycobacteria are not commercially available at this time. When used in the past, these skin tests provided some guide to the specific mycobacterial etiology.[140] In general, skin test reactions involving 5–10-mm diameter areas of skin are suggestive of atypical mycobacterial lymphadenitis, whereas reactions af-

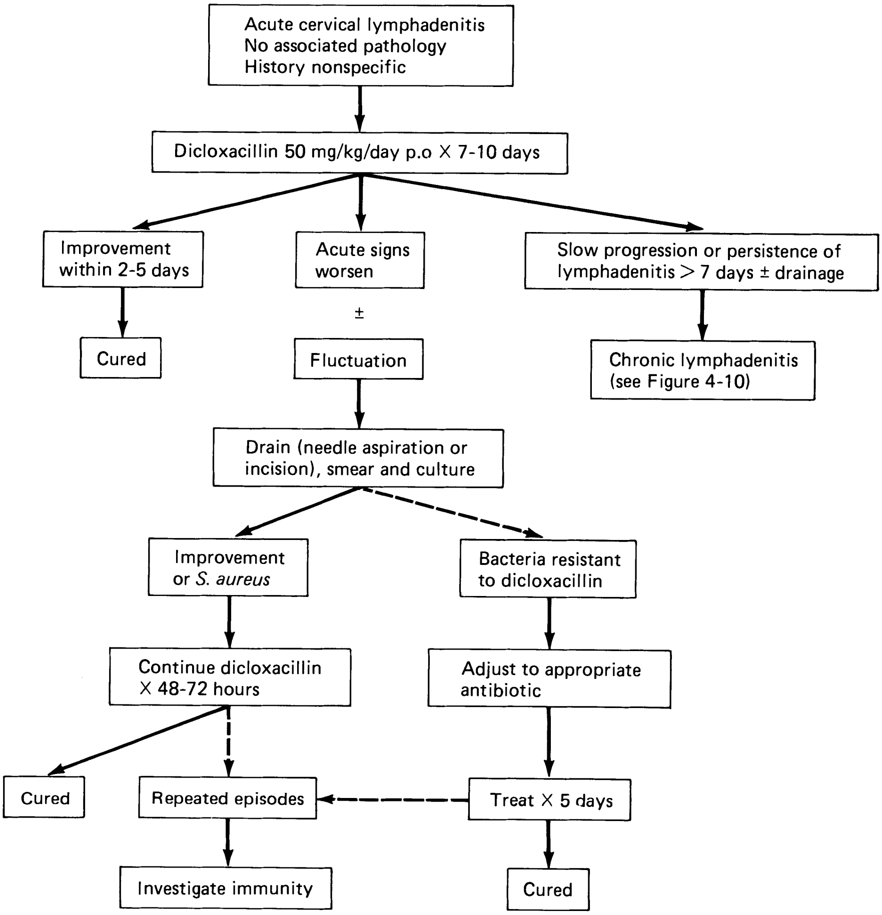
Acute cervical lymphadenitis
No associated pathology
History nonspecific
Dicloxacillin 50 mg/kg/day p.o X 7-10 days
Improvement within 2-5 days
Acute signs worsen
Slow progression or persistence of lymphadenitis > 7 days ± drainage
Cured
±
Fluctuation
Chronic lymphadenitis (see Figure 4-10)
Drain (needle aspiration or incision), smear and culture
Improvement or *S. aureus*
Bacteria resistant to dicloxacillin
Continue dicloxacillin X 48-72 hours
Adjust to appropriate antibiotic
Cured
Repeated episodes
Treat X 5 days
Investigate immunity
Cured

Figure 4–9. Diagnostic evaluation of acute cervical lymphadenitis (less than seven days duration).

fecting areas greater than 10 mm also suggest the diagnosis of tuberculosis.

The evaluation of more chronic causes of lymphadenopathy is outlined in Fig. 4-10. In the head and neck, particular attention should be given to tularemia with or without signs of oropharyngeal inflammation. This is best diagnosed by measuring the titer of agglutination antibody to tularemia antigens in the patient's serum. Peripheral blood eosinophilia may suggest the presence of toxocara, and atypical lymphocytes, Epstein-Barr virus. Cat-scratch disease is best diagnosed by history of contact and exclusion of other causes (Fig. 4-11). Poorly standardized skin test antigens have been used; however, estimates of the test's specificity and sensitivity are impossible. Aspiration of painful, fluctuant nodes is often beneficial; however, no specific therapy is available.

Atypical mycobacterial disease, tuberculosis, neoplasia, histiocytosis,

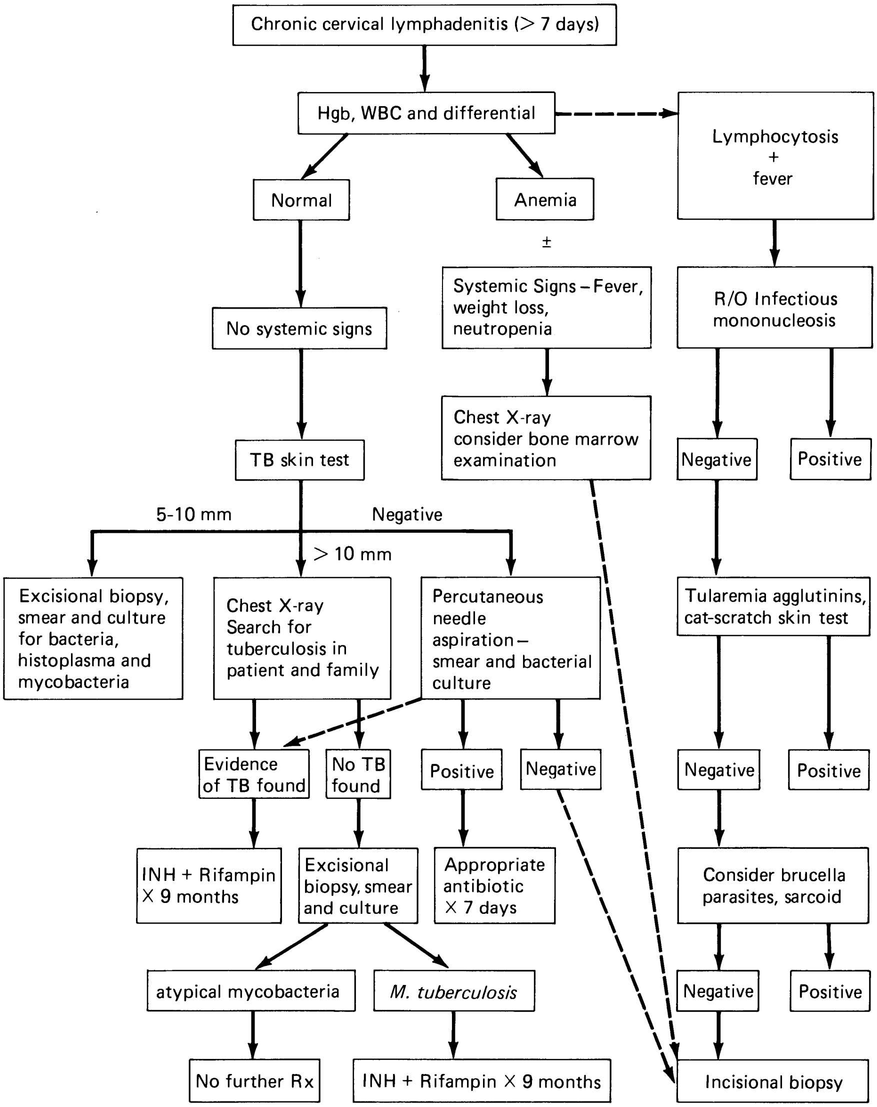
Chronic cervical lymphadenitis (> 7 days)
Hgb, WBC and differential
Normal
Anemia
±
Systemic Signs – Fever, weight loss, neutropenia
Lymphocytosis + fever
No systemic signs
Chest X-ray consider bone marrow examination
R/O Infectious mononucleosis
TB skin test
Negative
Positive
5-10 mm
Negative
> 10 mm
Excisional biopsy, smear and culture for bacteria, histoplasma and mycobacteria
Chest X-ray Search for tuberculosis in patient and family
Percutaneous needle aspiration – smear and bacterial culture
Tularemia agglutinins, cat-scratch skin test
Evidence of TB found
No TB found
Positive
Negative
Negative
Positive
INH + Rifampin X 9 months
Excisional biopsy, smear and culture
Appropriate antibiotic X 7 days
Consider brucella parasites, sarcoid
atypical mycobacteria
M. tuberculosis
Negative
Positive
No further Rx
INH + Rifampin X 9 months
Incisional biopsy

Figure 4–10. Diagnostic evaluation of chronic cervical lymphadenitis (more than seven days duration).

and, occasionally, toxoplasmosis can best be diagnosed by histopathologic examination of lymph node. Considering the wide differential diagnosis and diverse microbiologic etiologies, a careful preoperative assessment is essential for appropriate processing and examination of the specimen. I am sure we have all had the unhappy experience of trying to piece together the diagnosis of one of these cases after a surgical procedure and "routine" microbiologic and histopathologic studies were carried out.

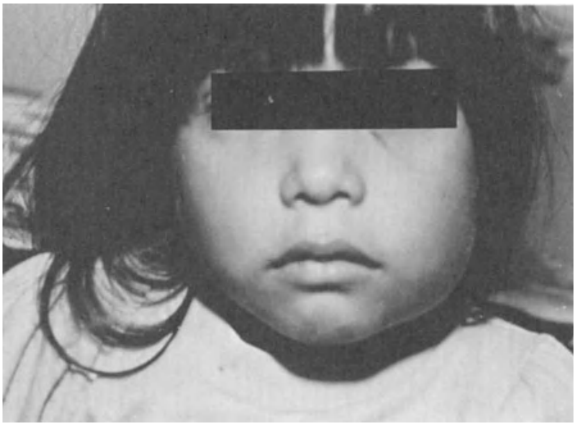

Figure 4–11. Inoculation site papule and preauricular and mandibular lymphadenitis after cat scratch.

Treatment

The initial approach to acute cervical lymphadenitis is based on the assumption that approximately two-thirds of cases are due to *Staphylococcus aureus* or group A Streptococcus. Hence, use of dicloxacillin 50 mg/kg/day, divided q 6 h, is a rational plan. Patients allergic to penicillin can be treated with cephalexin 75 mg/kg/day in four divided doses. The node should be measured and the patient's course followed. If there is no clinical improvement within 72 h, consideration of drainage by incision or needle aspiration should be given. This is particularly appropriate for advanced staphylococcal lympadenitis, where viable organisms may be found in drainage material despite the administration of potent antistaphylococcal antibiotics. Drainage will usually reduce morbidity.

Patients with more chronic lesions, as discussed above, require more extensive diagnostic workup and therapy based on the specific etiology. In North America, many of these patients have atypical mycobacterial disease or reactive hyperplasia secondary to repeated upper respiratory infections. Excision is curative for atypical mycobacterial lymphadenitis,[192] whereas 9 months of antituberculosis therapy with two drugs (e.g., isoniazid and rifampin) should be used for tuberculous lymphadenitis.[244] Biopsy is unrewarding in up to 80% of cases of chronic lymphadenopathy.[113] The rationale often used is that the surgical approach will save an expensive and arduous diagnostic workup. The truth is that the histopathologic diagnosis in many of these cases is nonspecific reactive hyperplasia or granulomatous changes. Subsequently, therefore, the detailed diagnostic studies are still needed, but the opportunity to examine the tissues for specific microbiologic causes has been lost in many cases. It is clear that the approach to diagnosis and management of lymphadenitis of the head and neck requires a detailed history, careful node measurements, and periodic observation by the physician, patient, and family. Repeated antibiotic courses and premature surgical interventions are often nonproductive.

Thyroiditis (Fig. 4-12)

Acute suppurative thyroiditis should be included in the differential diagnosis of anterior cervical inflammatory lesions, such as cellulitis, lymphadenitis, and abscess.[19] This rare condition is manifest by severe anterior neck pain, swelling over the area of the thyroid, and systemic

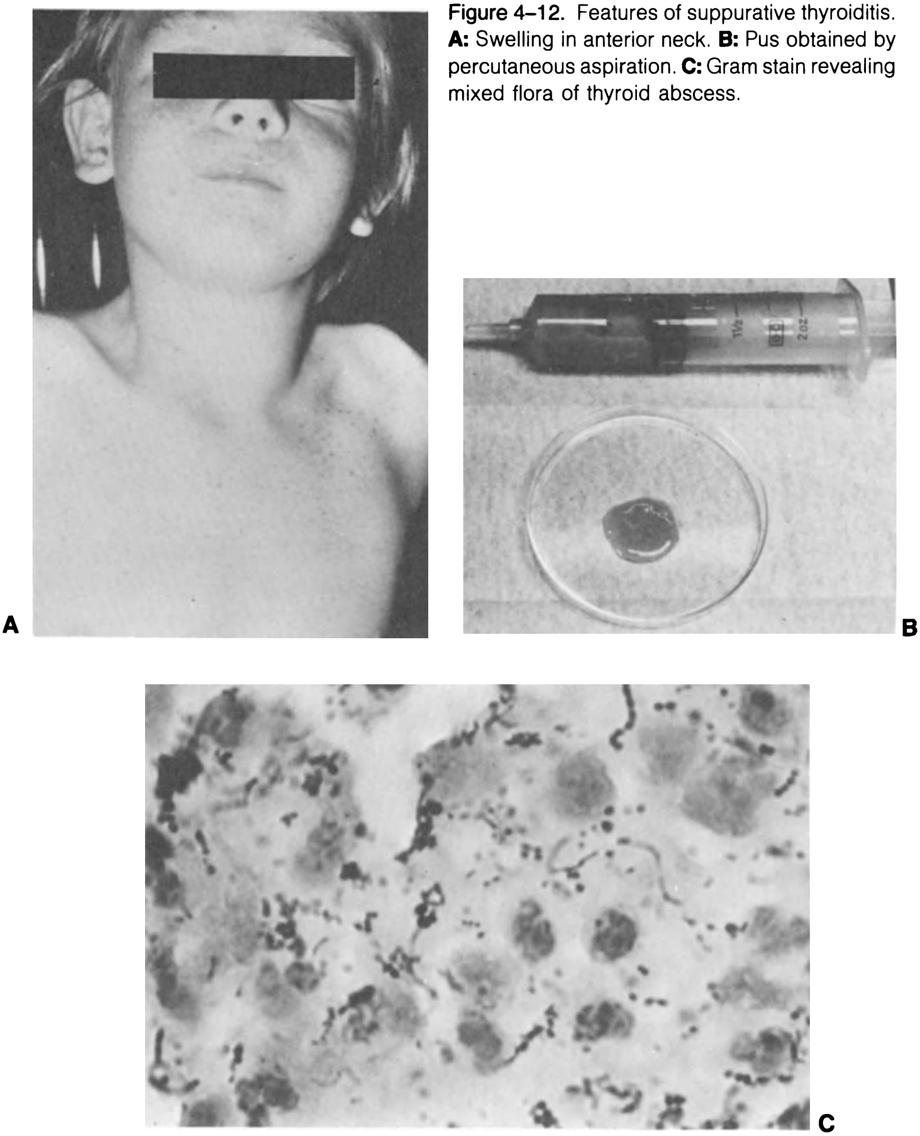

Figure 4–12. Features of suppurative thyroiditis. **A:** Swelling in anterior neck. **B:** Pus obtained by percutaneous aspiration. **C:** Gram stain revealing mixed flora of thyroid abscess.

toxicity.[1] Males seem more commonly infected and the ages of patients reported have been between 3 days[152] and 12 years.

Etiology

The infection is usually due to mixed anaerobic flora, suggestive of invasion by oral bacteria.[233] *Staphylococcus aureus* may be present alone or, more commonly, anaerobic streptococci and Bacteroides are also found. Unusual infectious causes have been reported in chronic granulomatous disease, including *Mycobacterium chelonei, Aspergillus fumigatus,* and Actinomyces.[82]

Diagnosis/Treatment

The diagnostic procedure of choice is percutaneous needle aspiration of the abscess site. Radionuclide scan with iodine-123 can be used to effectively localize the infection in the thyroid.[259] Appropriate antibiotic therapy includes penicillin and oxacillin initially, which should be adjusted based on gram stain, the results of skin testing, and microbiologic data. These children are usually euthyroid and the prognosis is excellent, with rapid defervescence after appropriate antibiotic therapy and drainage.

Parotitis

Except as a manifestation of mumps virus infection, parotitis is a relatively uncommon condition in children. Lymphadenitis is sometimes confused with inflammation of the parotid, since the lower lobe of the parotid gland may extend below the angle of the jaw. Generally, however, swelling, tenderness, and erythema over the posterior one-third of the mandible and under the tip of the ear lobe are characteristic of parotid inflammatory disease.

Parotitis can be divided into three main categories: acute, chronic, and recurrent. The causes of acute parotitis listed in Table 4-16 can be divided into viral and suppurative types. Viral parotitis is classically due to mumps virus and usually associated with fever, acute tenderness of the parotid glands, and generalized malaise. A mumps-like parotid swelling may also be due to parainfluenza virus[145] and, occasionally, influenza,[28] coxsackie, or ECHO virus infections. Lymphadenopathy, jaw tumors, masseter muscle swellings, and infantile cortical hyperostosis can be confused with parotitis.

Mumps

Mumps is generally a viral infection of school-age children, although the disease may occur at any age. As many as half of the infected individuals

TABLE 4-16. Causes of Parotid Enlargement

- Viruses
  - Mumps
  - Parainfluenza
  - Influenza
  - Cytomegalovirus
  - Coxsackie
  - ECHO
  - Lymphocytic choriomeningitis
- Bacteria
  - *Staphylococcus aureus*
  - Streptococcus
  - Peptostreptococcus
  - Actinomyces
  - Mycobacteria
  - Rat-bite fever (*Streptobacillus moniliformis*)[178]
- Fungi
  - Histoplasma
- Other
  - Drug hypersensitivity (e.g., iodides, lead, mercury, nitrofurantoin)[167]
  - Sarcoid
  - Tumors
  - Pneumoparotitis
  - Trauma
  - Parotid duct obstruction
  - Recurrent idiopathic parotitis

seroconvert after a mild nonspecific illness or without any signs of infection at all. The majority of symptomatic patients have fever, parotitis, and malaise, usually lasting for 3–4 days. The younger the child, the better the infection is tolerated.

Complications of Mumps. Complications of mumps generally reflect involvement of tissues and organs other than the parotid glands. These are the meninges, thyroid, pancreas, testes, ovaries, and occasionally other areas. Many of the reports merely describe the association of signs or symptoms with mumps infection. Hence, although glomerulonephritis, presternal edema, arthritis, conjunctivitis, mastitis, and myocarditis[35] have been reported in association with mumps, cause and effect are often not proven.

As many as 50% of children infected with mumps virus may have cerebrospinal fluid pleocytosis, sometimes with a low sugar concentration and normal, or slightly elevated, protein concentration. Many have no symptoms or only headache, while others manifest stiff neck, vomiting, and, rarely, seizures. One report describes development of aqueductal stenosis in a 10-year-old 3 weeks after mumps infection.[240] Crude estimates of complications are as follows: meningoencephalitis 3/1000 cases (1.4% of these die); hearing loss (mild 90%, moderate 9%, severe 1%) 1/20,000; orchitis 25 % in men over 15 years of age.[117] Older patients may have severe pain and tenderness due to involvement of the testes, ovaries, thyroid, or pancreas. There is little that can be done in these situations, except for the administration of analgesics and rest.

Prevention of Mumps. At present, mumps can be prevented in the vast majority of infants and children by the administration of live attenuated mumps virus vaccine beyond the first year of life.[117] Although the disease is generally mild, the vaccine is one of the safest and most effective available.[100] Its widespread use will continue to decrease the morbidity and mortality associated with mumps infections.

Mumps virus can be excreted in saliva and urine from 7 days before illness to 14 days thereafter. Mumps immune globulin is not effective in preventing or treating the disease. Although mumps vaccine can be safely administered to susceptible subjects after exposure, the efficacy of this procedure has not been proven.

Acute Suppurative Parotitis

This is an unusual but serious condition seen predominantly in newborns,[128] the elderly, and in immunocompromised patients.[127] The disease is heralded by acute tenderness of the parotid gland associated with systemic signs of infection and often with purulent discharge from the parotid duct. *Staphylococcus aureus* is the most common cause, although streptococci, anaerobes, and Actinomyces may be responsible.[6] Generally the diagnosis is established by gram smear and culture of purulent material obtained from Stensen's duct or from material obtained by percutaneous needle aspiration of the infected gland. The latter procedure is more useful because it avoids contamination of the specimen by oral flora. The condition is best treated by a combination of antibiotic therapy (e.g., dicloxacillin 75 mg/kg/day divided q 6 h orally or oxacillin 150 mg/kg/day q 6 h intravenously) and surgical drainage. Early in the course, antibiotic therapy alone may suffice; later on surgical drainage can be lifesaving. Surgery in this area is often difficult because the gland may envelop several branches of the facial nerve.

Chronic Parotitis

Chronic parotitis is a rare condition of infancy and childhood today. It can be caused by *Mycobacterium tuberculosis*, atypical mycobacteria, Actinomyces, and can also be seen in sarcoidosis. The etiologic diagnosis can be suggested by appropriate skin testing, but often depends on specific histopathologic examination of biopsied material. The management and treatment of these conditions are similar to those outlined above for lymphadenitis.

Recurrent Parotitis

Recurrent parotitis is a frustrating condition for the patient and his family, as well as for the physician. Unfortunately, little is known about its pathogenesis and etiology.[116] The condition is one of variable expression; hence reports of therapeutic efficacy must be judged skeptically. Some of these patients have repeated episodes and then the condition resolves, while others may stop having recurrences at the onset of puberty. Material obtained by careful aspiration and culture of duct fluid is rarely different from normal oral flora. In some circumstances tuberculosis may be causative; in others, trauma secondary to habitual chewing of the buccal mucosa has been implicated.[255] Unusual causes include the playing of wind instruments and congenital or acquired obstruction of the parotid duct.[245] These are generally unilateral conditions and can be diagnosed by careful history, sialography, and physical examination. Despite many attempts to define host abnormalities, the condition remains enigmatic in the vast majority of cases. The physician can be of most service if he excludes treatable causes of recurrent parotitis, such as tuberculosis, atypical mycobacteria, obstruction, and neoplasia. Subsequently, a generous dose of reassurance and supportive care (mild analgesics and warm compresses) will often suffice. Although some clinicians use short courses of antibiotics directed against oral flora (e.g., penicillin or cephalexin), there are no data to support the additional risk attendant to the use of these therapies.

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5

Lower Respiratory Infections

General Considerations

Many of the clinical features of upper respiratory infections outlined in the previous chapter are characteristic of lower respiratory infectious diseases of children as well. For example, respiratory syncytial and parainfluenza virus infections are most frequent in the second year of life and most severe in the first. The incidence of these infections varies with circumstances, including the size of the family, use of day care centers, geography, nutritional status, and socioeconomic conditions.[30] Children in smaller families with less frequent exposure to respiratory infection acquire disease less often. Atopy may be an important predisposing factor in some children.[165] Many upper respiratory viral infections cause transient lower respiratory alterations in airway dynamics; however, these generally last only a few weeks and long-term complications are unusual. Frequent and recurrent lower respiratory infections may set the stage for chronic bronchitis, reactive airway disease (manifest as recurrent cough and/or wheezing), bronchiolitis obliterans, and bronchiectasis.[235] In certain hosts, progressive pulmonary injury and respiratory impairment are associated with recurrent and persistent lower respiratory infection (Table 5–1). It is rare for a respiratory infection to involve exclusively the lungs, tracheobronchial tree, or laryngeal area, since components of upper and lower respiratory infection usually coexist. Thus, although we shall try to limit the discussion to pulmonary parenchymal disease, the overlap with bronchitis, pleuritis, and upper respiratory infections should be kept in mind.

Pathogenesis/Etiology

Viruses, the commonest cause of lower respiratory infection, induce ciliary dysfunction and respiratory epithelial cell damage in almost all cases.

TABLE 5–1. Conditions that Predispose to Recurrent Lower Respiratory Infection and Progressive Lung Damage

- Cystic fibrosis
- Shwachmann syndrome
- α_1-Antitrypsin deficiency
- Immune deficiencies
- Hypo/dysgammaglobulinemias
  - Chronic granulomatous disease
  - Phagocyte dysfunction syndromes
  - Immotile cilia syndromes
- Recurrent aspiration
- Idiopathic
  - Gastroesophageal reflux
  - Neurogenic
  - Tracheoesophageal fistula

Many of the signs and symptoms of bronchitis and bronchopneumonia are referable to this injury. This also sets the stage for secondary bacterial, mycoplasmal, and occasionally (e.g., in the debilitated or immunocompromised host) fungal infection. The severity of lower respiratory infections seems increased in obese patients and in those exposed to air pollutants, including inhaled cigarette smoke. Frequency of infections is greatest in certain closed populations, such as hospitals and institutions for the mentally retarded, as well as in day-care centers with high population densities. Zoonotic infections, such as tuberculosis, psittacosis, tularemia, Q fever, and hydatid disease, may be transmitted to humans from animals of various species, with resultant pulmonary manifestations.[21]

Clinical Manifestations

The clinical manifestations of lower respiratory infection in infants and children are extremely diverse and upper respiratory signs are often present as well. Some infants and children have only short-lived or persistent cough, without systemic signs of illness and little apparent morbidity. Sleeplessness and anxious parents may be the only problem in these cases. Contrast this with the other end of the spectrum, where young infants present with acute respiratory failure and significant CO_2 retention ($>$ 60 mm Hg). These infants are often exhausted, have repeated episodes of apnea, and may have convulsions.[293] The commonest cause of this syndrome in young infants is respiratory syncytial virus.

Lower respiratory infection is suggested most specifically by tachypnea, indrawing, and cough. In fact, sleeping respiratory rates may be the most sensitive indicator of the severity of these infections. Grunting and nasal flaring in the newborn and young infant, and wheezing, pleuritic pain, shortness of breath, and cyanosis in children of all ages, may also suggest lung involvement.

Other signs of lower respiratory infection are nonspecific and include fever, tachycardia, malaise, and anorexia. Although chills may be present, they more commonly reflect systemic viremia or bacteremia, features often associated with lower respiratory infection. In such patients, extrapulmonary manifestations of respiratory infections should be sought. These may be suggested by irritability (or lethargy), anxiousness, or disorientation; however, these may also be signs of impending respiratory failure.

Diagnosis

The etiologic diagnosis of lower respiratory infection often depends on epidemiologic information and clinical judgment. The first concerns the time or season, the viruses prevalent in the community (e.g., influenza outbreaks), and pertinent exposure history. For example, exposure to pertussis clearly facilitates that diagnosis. Less obvious is exposure to an adult with pharyngitis, conjunctivitis, herpangina, pleurodynia, etc., some of the more subtle manifestations of viral infections that may manifest as lower respiratory infection in the exposed contact.

Clinical judgment rests on knowledge of the syndromes, as outlined below. Thus, recognition of respiratory syncytial virus is supported by a clinical diagnosis of bronchiolitis and that of parainfluenza by a diagnosis of croup. Certainly, the virologist's task is made easier if he is provided with an etiologic diagnosis based on clinical information. This is becoming increasingly vital to allow better selection of techniques used to culture viruses and to obtain a rapid diagnosis of viruses [e.g., immunofluorescence, electron microscopy, or enzyme-linked immunosorbent assay (ELISA) methods]. Specific etiologic diagnoses can also be made for mycoplasma, chlamydial, mycobacterial, and fungal causes of lower respiratory infection, using microbiologic and serologic techniques.

Therapy

Many formulations are used to treat cough and the oft-associated signs of upper respiratory infection seen in these patients. These are very much overprescribed! Many are of questionable efficacy and may be unsafe, particularly in infants, in whom idiosyncratic drug effects can cause hypertension, apnea, lethargy, irritability, or gastrointestinal side effects.[21] Cough is an important host defense and, generally, should not be treated except at bedtime, and only when it interferes with sleep.

Before considering specific antimicrobial therapy, the clinician should pay attention to the need for respiratory support. Intermittent positive-pressure ventilation or other ventilatory support may be life-saving in infants with apnea and other signs of acute respiratory failure. This is most commonly seen in the first year of life, but may also be a component of bronchiolitis and croup in older children. Oxygen requirements should be determined by clinical examination (e.g., the presence of cyanosis, tachypnea, and dyspnea) and by arterial blood gas measurements. The use of oxygen is beneficial in hypoxemic patients, but its overuse may decrease bacterial clearance by pulmonary alveolar macrophages as well as induce toxicity to cilia and respiratory epithelial cells. Antimicrobial therapy is based on the clinical diagnoses and its usual etiologies.

Prevention

Respiratory syncytial virus and rhinoviruses are spread most commonly by direct contact, whereas influenza and adenoviruses are spread by the aerosol route as well. To prevent the former, wearing gowns and washing hands are useful measures, whereas masks should be added for prevention of aerosolized spread. Among predominantly respiratory infections, active immunization is restricted to pertussis, tuberculosis, and influenza (see Chapter 3) and chemoprophylaxis and therapy to influenza A.

Knowledge of the etiology and the patterns of shedding of respiratory pathogens can also aid decisions about management and control of these infections. Unfortunately, the latter are not easy to achieve because approximately one-third of patients can excrete respiratory viruses for up to 6 days before the onset of clinical illness. The maximum period of excretion occurs within the first week of illness; however, up to 75% of patients are still excreting respiratory viruses at the end of the first week and 30% at the end of the second week.

The reader is referred to Chapter 3 for consideration of respiratory infections in newborns. Specific features of clinical syndromes of lower respiratory infections in infants and children are outlined below.

Croup

Infections of the upper and lower respiratory tract can be roughly divided according to anatomic criteria; however, some overlap is obvious.[80] In the case of croup, this is particularly evident. Some patients have predominantly laryngeal involvement and their illness is often classified as laryngitis, although they occasionally have a "barking" cough. In others most of the inflammatory changes are present in the subglottic area, giving the more classic feature of croup (inspiratory stridor and barking cough). Still others have subglottic edema and tracheitis or bronchitis, or both. Thus, the clinical entity of croup is derived from a group of lower respiratory infections that may involve the tracheobronchial tract from the larynx to the bronchi, and even the pulmonary parenchyma. No wonder there is confusion! Moreover, some authors use the term "laryngotracheobronchitis" to refer to croup,[326] whereas others reserve the same term for patients with bacterial or viral tracheitis superimposed on laryngobronchitis.[63]

Recognizing these difficulties in classsification, we will have to define our terms very clearly. We will consider laryngitis as a predominantly upper respiratory infection almost exclusively due to common respiratory viruses, and usually associated with the common cold syndrome. Croup will be discussed as a disease where the pathology involves predominantly the subglottic area and is characterized by a barking cough and inspiratory stridor. Tracheitis will be discussed separately and is defined as an infection of the trachea just below the subglottic area, predominantly due to bacteria, and often of a severe nature. Tracheobronchitis, on the other hand, is less severe, can be either viral or bacterial, and has several different modes of pathogenesis. Tracheobronchitis may include bronchopneumonia in some patients.

Epidemiology

Croup can be classified as one of two types. One, "spasmodic croup," usually occurs suddenly at night, without a prodrome or fever, and is often seen in atopic individuals. "Croup" is the term reserved for the most common expression of subglottic edema due to respiratory infection. It is often called laryngotracheitis as well. Both types occur predominantly in the 3-month-old to 3-year-old age group and are most frequently seen in the fall and winter seasons.[80] The condition is extremely common in North American populations, where it is usually caused by conventional respiratory viruses, especially parainfluenza. In developing countries, croup may also be seen with measles, diphtheria, and occasionally, pertussis.

Etiology

As mentioned above, the exact cause of spasmodic croup is unclear, although it appears to occur more frequently in patients with a personal and family history of atopy, and specifically asthma. The triggering event, however, may still be infection with common respiratory viruses. Those most commonly associated with classic croup are parainfluenza viruses 1 and 3, and influenza viruses. Approximately 65% of cases in young infants are due to parainfluenza virus 1; influenza virus and *Mycoplasma pneumoniae* are causative in children over 5 years of age.[82] Croup may also be seen with measles, respiratory syncytial virus, diphtheria, and, very rarely, nontypable *Haemophilus influenzae* or *Chlamydia trachomatis.*[230]

Clinical Manifestations

Croup is a frightening experience for most parents and, often, for the children as well. Spasmodic croup begins dramatically, with little advance warning. The patient is usually not febrile and awakens at night with inspiratory stridor and a barking cough. The sound of this cough is often likened to the bark of a seal. Croup, on the other hand, often occurs after 2 or 3 days of upper respiratory infection, usually with coryza and mild cough and fever. The cough becomes more barking in nature and inspiratory stridor becomes prominent. There is waxing and waning of these signs over a few days in cases of croup, whereas spasmodic croup often improves within several hours. The signs of classic croup are worse at night and are much less responsive to the effects of humidity than is spasmodic croup. Some patients have hoarse voices, or actually lose their voices completely. Rarely, the clinical course progresses to severe respiratory obstruction that can be life-threatening. Pulmonary edema has been reported in some of these children.[160]

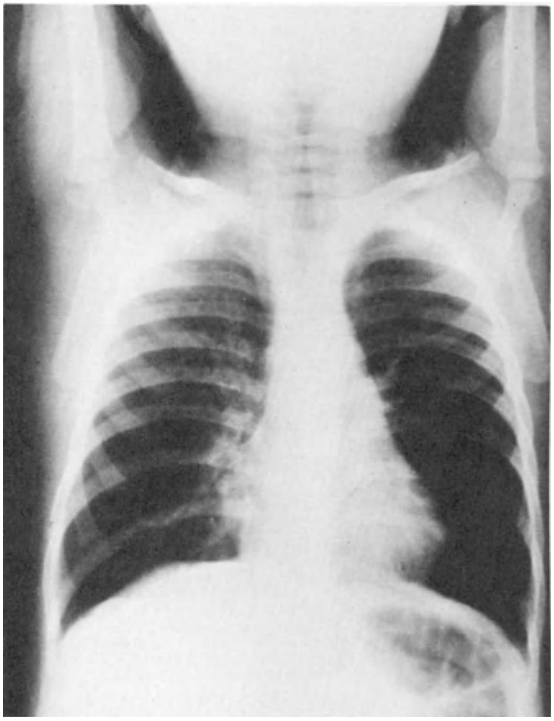

Figure 5–1. Tracheal narrowing in the subglottic area in a patient with croup.

Diagnosis

The clinical picture and characteristic cough suggest the diagnosis in most cases. Some of the clinical features are also compatible with epiglottitis. In these cases it is particularly useful to obtain a lateral X-ray of the neck region in which the epiglottis and subglottic area can be visualized.[232] A tapering of the swollen subglottic area and a normal-appearing epiglottis are usually seen (Fig. 5–1). The white blood cell count is rarely helpful in diagnosis of croup, except to rule out the presence of bacterial tracheitis, in which the white blood cell count is often elevated and shifted to the left. The serum C-reative protein concentration is normal in croup but elevated in epiglottitis.

Treatment (Table 5–2)

Spasmodic croup is best treated by humidification. Parents can be instructed to take the child out in the cool, moist night air (if those conditions exist) or to use the cold running shower to create similar conditions in the bathroom. This procedure, or emesis, is often associated with dramatic improvement in infants with spasmodic croup. Use of cool vapor in the child's room may be all that is necessary to treat the vast majority of infants with this condition. They are often dramatically improved by the next day.

TABLE 5–2. Management of Croup

- Spasmodic Croup
  - Cool and humid air
  - Reassurance and observation
  - If prolonged, rule out foreign body, congenital anomaly, diphtheria
- Croup
  - Nonhospitalized patients
    - Cool and humid air
    - Reassurance and observation
    - Antipyretics, if greater than 39°C
  - Hospitalized patients
    - As above
    - Dexamethasone 1–1.5 mg/kg (maximum 30 mg) intramuscularly; total of two doses 2 h apart
    - Monitor sleeping respiratory rate
    - Oxygen (first measure PO_2, PCO_2)
    - Racemic epinephrine 2.25% by aerosol
    - Decision to intubate based on serial clinical observations and measurements of respiration, pulse, blood gases, and chest X-ray findings
    - Rule out bacterial tracheitis if course severe and/or prolonged

Those patients who do not respond in this way and appear to have a more prolonged course should be examined for other conditions. These include aspiration of foreign body, diphtheria, angioedema, or congenital abnormalities of the tracheobroncheal tree (e.g., laryngeal web). Occasionally, epiglottitis, bacterial tracheitis, or posttraumatic laryngeal edema may be confused with acute croup.

Criteria for hospitalization for spasmodic and classic croup should include many considerations, such as proximity of the home to the hospital, ability of the parents to cope and follow instructions, severity of the condition, and the age of the patient. Respiratory rate is a critical indicator of hypoxemia and its careful measurement during sleep or rest can be used to guide both parents and physician in the management of these patients.

Classic croup (acute laryngotracheitis) is treated differently. The use of steroids is controversial, although there is agreement that this should be reserved for hospitalized cases. Although five of the nine published studies showed a beneficial effect of steroids (a diminution of hospitalization by an average of 1 day in a total of 2–3 days), shortcomings in their design limit their interpretation.[245] A major problem is the lack of differentiation of spasmodic croup from acute laryngotracheitis. A sixth published study did stratify patients appropriately and, in fact, confirmed the benefit of steroids in treatment of acute laryngotracheitis (croup).[11] However, a seventh showed benefit only for spasmodic croup.[189] Many choose steroids for hospitalized patients with laryngotracheitis because of its low toxicity and potential usefulness as an adjunct to cool mist, oxygen, and careful observation. If used, dexamethasone 1–1.5 mg/kg (maximum 30 mg) should be administered intramuscularly as soon as the diagnosis is made in patients having moderate to severe involvement. This should be repeated 2 h later. In those mildly ill, and those who can be observed at home, the pain and the small risk of the medication do not seem justified. A clinical score used to guide the physician in his judgment of the severity of croup has also been developed.[326]

The other mainstays of treatment for croup include humidification, supplemental oxygen, and racemic epinephrine. In the former case, humidification can be carried out at home by use of a vaporizer set at cool and in hospital by use of croup rooms, hoods, tents, or masks. Intermittent positive-pressure breathing is useful in some patients, but the physician should always weigh the risks of inducing anxiety in such patients and choose the procedure that is least likely to do so. Increased respiratory rate often indicates the need for oxygenation. Determination of blood gases should be made in order to document objectively the status of the patient before oxygen is prescribed. It may be necessary to repeat this during the course of observation. One of the most sensitive indices of hypoxemia is an increasing respiratory rate during sleep.[245] Cyanosis, anxiety, and restlessness are late signs.

Moderate and severely ill patients should also receive racemic epinephrine.[326] Usually 2.25% (0.5 ml in 4 ml of normal saline) is administered by nebulization through a mask or by use of intermittent positive-pressure breathing. An interval of 30 min should be allowed between treatments. This type of treatment should be reserved for hospitalized patients, since rebound to the pretreatment status may occur. It should be remembered that, although this discussion includes dexamethasone and racemic epinephrine treatment, the vast majority of infants with croup can be managed at home with humidification, fluids, and antipyretic therapy. Antibiotics are not indicated in croup (laryngotracheobronchitis) or in spasmodic croup.[330]

Croup in children over the age of 5 years may be due to influenza, *Mycoplasma pneumoniae*,[82] or bacterial tracheitis.[209] Since drug treatments include amantadine, erythromycin, and antistaphylococcal drugs, respectively, a specific diagnosis should be sought early and specific treatment prescribed.

Prognosis

Spasmodic croup is a benign condition in which recovery is usual within 8–24 h. The condition can recur and is particularly likely to do so in patients with strong allergic histories and in those with congenital or acquired narrowing of the laryngeal and subglottic areas.

The prognosis of classic croup (acute laryngotracheobronchitis) is also benign. Most patients recover within 2–4 days. A few require hospitalization for 1 or 2 days, and a much smaller number may require intensive care observation. Of these, some require intubation and assisted ventilation. It is difficult to predict which patients will be most severely affected; therefore, frequent observation is necessary. Although useful diagnostically, the lateral neck roentgenogram does not correlate well with severity of the clinical illness.

Patients with persistent and rapidly recurring syndromes should be examined for the presence of foreign body or congenital anomalies of the trachea and larynx. Allergic patients and those with previous episodes of severe croup are more likely to have stormy courses. When croup does recur in a patient, as many as 30% may indeed have reactive airway disease and some of these develop asthma later in life.[365] In one study 35% of 96 children examined 8.5 years after hospitalization for croup had evidence of increased bronchial reactivity, although atopy was not a prominent feature.[95] One implication is that these children may be at risk of chronic obstructive airway disease as adults. They should be strongly discouraged from smoking and from choosing occupations and environments with increased air pollution.[95]

Tracheitis

Pathogenesis/Etiology

Some patients with croup are refractory to the initial treatment described above. Their course may be progressive or they may appear to be doing well and then their signs begin to worsen. Fever, stridor, and airway obstruction are prominent. Tracheitis should be suspected. In this condition the trachea becomes infected and inflamed immediately below the subglottic area. A few of these patients have viral infections,[80] but many appear to have bacterial superinfections of a primary viral laryngotracheitis as well. This is a serious condition and needs to be diagnosed accurately and quickly. The usual causes are *Staphylococcus aureus,*[149] group A Streptococcus, nontypable *Haemophilus influenzae,*[174] and respiratory viruses. Inhalation of heated gases and aerosols can also cause acute tracheitis.[184]

Clinical Manifestations/Diagnosis

The patients appear acutely ill, the temperature ranges from 37 to 40°C,[80] they show no response to racemic epinephrine administered by intermittent positive-pressure breathing, and their white blood cell count becomes elevated and shifted to the left, with 13–15% band forms reported. Blood cultures are usually negative, but endotracheal aspiration of the subglottic area reveals mucopurulent material in which neutrophils and one of the above organisms may be seen on gram smear.[174] Direct examination of this area and establishment of a competent airway are important.

Treatment

The treatment for acute tracheitis includes careful attention to the airway, oxygen, tracheal suctioning, and, often, endotracheal intubation or tracheostomy. Antistaphylococcal antibiotics, such as oxacillin 200 mg/kg/day, should be given intravenously. Gram stain results may suggest the need for chloramphenicol, moxalactam, or cefotaxime as well. If the diagnosis proves to be infection with group A Streptococcus or other bacterial pathogens, the antibiotics can be adjusted appropriately. Intensive care nursing, observation, and intubation are rarely required for longer than a 48-h period. A slower response may indicate that anoxic brain injury has occurred. Antibiotics can be given orally when the patient can cooperate and should be continued for 5–7 days.

Two of 18 patients with acute bacterial tracheitis reported in the recent literature died.[208] The condition should be aggressively diagnosed and managed.[299]

Tracheobronchitis

Tracheobronchitis can occur as an extension of croup and tracheitis, or, more commonly, as a distinctive entity. In the community, this is predominantly a viral condition, usually due to parainfluenza and respiratory syncytial viruses in young infants and influenza A and B viruses and *Mycoplasma pneumoniae* in older patients. In such situations, these etiologies account for 85% of the cases.[60] Occasionally, *Streptococcus pneumoniae* infections, tuberculosis, histoplasmosis, and other causes of lower respiratory infection may manifest predominantly as tracheobronchitis. The condition is poorly defined clinically, but is characterized by deep cough and the presence of rhonchi. The chest X-ray either may be normal, or patchy pneumonic infiltrates may be seen; but this is also true in cases of croup and tracheitis. Thus, the overlap with bronchopneumonia and pneumonia is obvious, but not surprising, considering the etiologies just mentioned.

Community-Acquired

Chapman et al. defined the causes and course of tracheobronchitis in approximately 5000 patients observed over 104 months.[60] These were predominantly white middle-class infants and children in North America, so their experience may not be entirely representative. Nonetheless, in that cohort, the peak incidence of community-acquired tracheobronchitis syndromes was seen in the first 2 years of life (approximately seven episodes/100 patients/year). This became much less frequent as the patients grew older (to approximately 1.6 episodes/100 children of 15 years and older).

The condition is usually benign and requires no specific therapy, despite the fact that cough may be present for several days to several weeks in some of these patients. Recurrent episodes of these types of infections are more commonly seen in patients with reactive airway disease, who are also at risk of developing asthma and asthmatic bronchitis later in life.

Hospital-Acquired

Tracheobronchitis may also be nosocomial. As in the community, patients with cystic fibrosis, chronic asthma, and other conditions with abnormalities of the tracheobronchial respiratory tract or its secretions are at increased risk of more severe illness or bacterial superinfections, or both.

In other situations, nosocomial tracheobronchitis can develop in patients who are intubated or have tracheostomies. These patients generally develop a tracheal flora comprised of bacteria similar to those in the oral cavity within 3–5 days after intubation or tracheostomy;[41] Candida may also be present. The term tracheobronchitis should be reserved for those patients whose secretions and clinical signs in association with such colonization subsequently increase in quantity and purulence (defined grossly and microscopically). A gram-stained smear should confirm the presence of neutrophils and bacteria. Quantitative bacteriology of these secretions may be useful in differentiating colonization from infection. Certainly, longitudinal observations of the characteristics of the inflammatory cells in the tracheobronchial secretions, as well as of the quality and quantity of the bacterial flora, are critical indices. In all cases, these must be considered together with clinical, ventilatory, and radiographic features. Pneumonia is considered likely if fever, peripheral leukocytosis, and bacterial concentrations > 100,000 colonies/ml are present.[262]

Chronically intubated and continually ill patients will be expected to have several episodes of nosocomial tracheobronchitis associated with recognizable bacterial and viral respiratory pathogens. These should be diagnosed by repeated gram and cytologic smears, cultures, and clinical and radiographic correlates. Short-term antibiotic therapy directed against treatable pathogens is a useful approach. Thus a 5-day course of ticarcillin and tobramycin can be very useful in quickly controlling *Pseudomonas aeruginosa* as a cause of acute tracheobronchitis in many of these patients. The temptation to use prolonged antibiotic therapy and aerosolized antibiotics should be resisted, since the development of unusual respiratory pathogens and resistant flora is a common consequence. The toxicity of aerosolized drugs should also be kept in mind.[343]

Bronchitis

Bronchitis is a poorly characterized condition in childhood.[327] Generally speaking, inflammation of the bronchi is manifest by cough and rhonchi and is present as a component of many infectious and noninfectious inflammatory syndromes of infancy and childhood. A condition referred to as "chronic bronchitis" in adults, defined as chronic productive cough for 3 months each year for 2 consecutive years without obvious underlying cause, is extremely rare in childhood.[322] Yet these adults must derive from a certain childhood population. How can these children be identified? Since the etiologies and pathogenesis of adult bronchitis are not well understood, this is a difficult task. However, certain patterns are evident. Thus, as children approach adolescence, it becomes obvious that some cough more frequently than others, particularly when acute upper respiratory infections are present. Sometimes this is evident earlier in childhood as well.

Pathogenesis

Several factors seem important in the development of bronchitis syndromes. There are genetic influences, as bronchitis seems to prevail in certain families. This is distinct from familial emphysema, with or without α_1-antitrypsin deficiency, which can also manifest as bronchitis, often with associated liver disease. Similarly, a family history of chronic cough should suggest the diagnosis of cystic fibrosis and the necessity to rule out tuberculosis and immunoglobulin deficiencies, all causes of chronic bronchitis and, in some cases, bronchiectasis. Patients with Kartagener syndrome may have bronchitis due to immotile cilia. Hereditary factors are important in some cases; in many others adult patients with chronic bronchitis and children with chronic cough are often members of lower socioeconomic classes, and come from homes and municipalities in which they are exposed to air pollutants, including cigarette smoke, and from families with frequent and recurrent respiratory infections. There is little fact to support the contention that sinusitis and postnasal drip are causes of chronic cough.[258]

Etiology

Bronchitis can arbitrarily be divided into acute and chronic forms. Acute forms generally last less than 3 weeks and are most commonly due to respiratory viruses, including respiratory syncytial, parainfluenza, adeno, and influenza viruses.[60] These are commonly seen in the first 2 years of life and in the winter months. *Mycoplasma pneumoniae* infection, pertussis, tuberculosis, and histoplasmosis may also be responsible.[60] In endemic areas, coccidioidomycosis and melioidosis may cause cough as well. Bacterial infection is rarely a cause of bronchitis in otherwise normal children. Hence, antibiotic therapy is generally not indicated.

Coughs lasting longer than 3 weeks also have many causes. Among these are asthma, cystic fibrosis, foreign body, and recurrent aspiration syndromes. The latter may be associated with a variety of congenital abnormalities, pharyngeal-esophageal incoordination, or gastroesophageal reflux. Neurologically impaired children may cough persistently in association with aspiration of feedings, gastric contents, and upper respiratory secretions. Tuberculosis; fungal infections; and pertussis, adenovirus, mycoplasma, and other chronic infections should also be given consideration in these patients. Occasionally parasites, such as Ascaris, Toxocara, Echinococcus, and Paragonimus may cause acute and chronic cough syndromes as the parasite migrates through the lung or becomes trapped in bronchial or peribronchial tissues. Bronchiectasis may also be present in the child with chronic cough. Known causes of bronchiectasis include postinfectious damage as seen after adenovirus infection, tuberculosis, repeated bacterial bronchitis and bronchopneumonia, foreign body aspiration, and parasitic infestations. Bronchiectasis may also be seen in patients with immunoglobulin deficiency and recurrent tracheobronchial infections.

Treatment

Since the etiology and pathogenesis of most acute bronchitis syndromes are clearly related to viral infection, symptomatic therapy directed at optimal nutrition and suppression of cough that interferes with sleep and eating seems appropriate. Use of expectorants, daytime cough suppressants, humidification, and antibiotics is unwarranted in most cases. In fact, humidified aerosols may carry opportunistic fungi, bacteria, and other allergens into the respiratory tract of these patients. Since their mucociliary clearance mechanisms are already impaired, this may compound the problem by stimulating further inflammatory reaction.

The treatment of acute and chronic bronchitis depends on elucidation of the underlying cause. Thus, the definition of a foreign body, tuberculosis, or immunoglobulin deficiency will lead to specific therapeutic approaches. Chronic bronchitis is often due to asthma in childhood and early adolescence.[70] A trial of bronchodilator therapy is often rewarding.

Prevention

Once underlying causes have been explored adequately, the clinician must consider the likelihood that these children will progress to chronic bronchitis of adulthood, a crippling condition in many situations. As mentioned above, favoring this development is a family history of this condition. In such a situation, smoking should be discouraged, the home and environment should be kept as free of air pollutants as possible, and excessive humidification in the patient's sleeping area should be discouraged. If the patient's cough is productive, it should be examined cytologically for the presence of polymorphonuclear leukocytes, suggesting bacterial superinfection, or the presence of eosinophils, suggesting an allergic component. In the former case, appropriate sputum cultures may reveal the cause of a specific intercurrent infection for which appropriate antibiotics can be prescribed. The aim is to prevent progressive bronchial damage. As in adults, once the stage of sputum production is reached and becomes chronic, the patient may require antibiotic therapy early in the course of respiratory infections.[322] A pattern usually develops in which the adolescent characteristically has fever, increased sputum production, and malaise associated with signs of upper respiratory infection. In these situations, *Streptococcus pneumoniae, Haemophilus influenzae,* and, occasionally, other gram-negative pathogens play important roles in the acute respiratory exacerbation. These patients should be treated with short courses of appropriate antibiotics, which can include amoxicillin, tetracycline, or trimethoprim-sulfamethoxazole.

In developing countries, breast feeding may decrease the frequency of acute bronchitis syndromes in infancy. This does not appear to be true in developed countries.[327] Patients with recurrent and chronic bronchitis should be immunized with pneumococcal and measles vaccines, and should be offered advice about smoking, air pollution, and appropriate medical care. Clearly, more research into the cause of chronic bronchitis of adults is needed before more specific steps in prevention, diagnosis, and management of this condition in childhood are possible.

Bronchiolitis

The manifestations of respiratory syncytial virus infections are diverse and depend, in part, on the patient's age and genetic predisposition.[356] The latter is illustrated by the frequency of wheezing and recurrent bronchiolitis in patients with reactive airway disease. Bronchiolitis, a specific expression of respiratory syncytial virus infection, occurs most frequently in the first 2 years of life. At this age infants have smaller peripheral airways when compared with those of adults. Once these airways have increased in size, and collateral ventilatory channels are better developed, atelectasis, hyperinflation, and hypoxemia are rarely associated with respiratory syncytial virus infections. Of course, the older patient with atopic asthma may have episodes of wheezing associated with upper or lower respiratory infection due to respiratory syncytial virus as well.

Epidemiology

The condition of bronchiolitis is most common between the ages of 2 and 6 months, but can also be seen in infants up to 2 years of age.[349] It is most frequent in the late fall and throughout the winter months in all parts of the world. Patients with underlying reactive airway disease (the only clue to this in young infants may be a positive family history of atopic asthma) are particularly prone to recurrent episodes of bronchiolitis and subsequent abnormalities of pulmonary function. The infection is often introduced into the house by an older sibling with a common cold syndrome or by an asymptomatic adult (Table 5-3). In hospital situations, adult caretakers may acquire respiratory syncytial virus without any symptoms or with a slight sore throat. Spread to other patients by direct close contact may result.

Etiology

Respiratory syncytial virus is by far the commonest cause of acute bronchiolitis in infancy.[151] The syndrome can also be seen with parainfluenza, adeno, influenza, rhino, and measles viruses. Rarely, *Mycoplasma pneu-*

TABLE 5-3. Manifestations of Respiratory Syncytial Virus Infection at Various Ages

Age	*Clinical Syndrome*
0–2 Months	Common cold with or without pneumonia
2–6 Months	Common cold with or without bronchiolitis
> 2 years	Common cold with or without wheezing
Adult	Common cold Pharyngitis Asymptomatic

moniae, pertussis, Chlamydia, or cytomegalovirus may be associated with this syndrome.[323]

Clinical Manifestations

This is a syndrome initially characterized by an episode of acute onset of expiratory wheezing, cough, retractions, and fever (temperature usually under 39°C) in a child (usually under 2 years of age) who has had rhinorrhea and fussiness associated with a common cold syndrome for a 2- or 3-day period.[223] Breathing difficulty may be of sudden onset and associated with flaring of the nostrils, suprasternal and intercostal retractions, cough, and wheezing. The nasal discharge is often clear, and examination of the chest may reveal respiratory wheezing with prolongation of the expiratory phase. Moist inspiratory rales may be present and the liver and spleen are frequently palpable due to hyperinflation of the intrathoracic compartment. The respiratory rate is often in the range of 60–80 respirations/min and the pulse concomitantly increased. The infant with a recurrent episode, and the older patient, may manifest a syndrome indistinguishable from allergic asthma. In isolated populations respiratory syncytial virus infections have been associated with considerable morbidity in infants manifesting both bronchiolitis and pneumonia.[240]

Diagnosis

The clinical signs mentioned above suggest the presence of either asthma or bronchiolitis. The cough is scanty and very unlike the staccato cough seen with chlamydia pneumonitis, or the inspiratory whoop and paroxysms associated with pertussis. Chest X-ray will confirm the presence of hyperinflation. The diaphragm is often flat, reflecting increased air trapping and accounting for the readily palpable liver and spleen. Although the white blood cell count may be elevated and even shifted to the left, this is nonspecific and rarely a useful finding. There is a family history of allergy in as many as 50% of cases. Some questioning to rule out the possibility of foreign body aspiration, hydrocarbon pneumonia, cystic fibrosis, tuberculosis, and psittacosis should be included in the workup.

Rapid virologic confirmation of respiratory syncytial virus infection is becoming more widely available by use of immunofluorescence[243] or ELISA[59] techniques.

Therapy

Patients are generally divided into two categories: those who have an underlying or acquired reactive airway disease and those who do not. The clinical status of the former patients is often improved by the use of bronchodilators. Generally, a test dose of epinephrine is given. If decreased wheezing and increased air movement results (this can be documented also by improvement in arterial blood gases), therapy with aminophylline (5 mg/kg every 6 h) may be useful.[349]

If bronchodilators are not helpful, therapy is strictly supportive. The major danger to the patient is hypoxemia; therefore, patients with rapid respiratory rates, clinical distress, and progressive disease should be examined objectively for the presence of hypoxemia and admitted to hospital if this is present. Patients with arterial oxygen pressures of < 70 mm Hg in room air require careful observation and supplementary oxygen.[349] Those with pressures of < 50 mm Hg, or those with arterial carbon dioxide concentrations of > 45 mm Hg, usually require intubation and assisted ventilation. Antipyretics, fluids, and careful observation for progressive hypoxemia and hypocarbia are essential elements in the management of these patients. Resting or sleeping respiratory rates are sensitive indices of the degree of oxygenation in such patients and these can be used to guide the frequency of blood gas determinations. The latter are most important for the management of appropriate oxygen supplementation. Neither antibiotic[106] nor corticosteroid[198] treatments have been found to be useful in bronchiolitis. However, the treatment of acute bronchiolitis is becoming a reality with the development of chemotherapeutic agents active against respiratory syncytial virus. Although ribavirin is effective, it must be administered by continuous aerosolization for a minimum of 3 days.[140]

Prognosis

As many as 50% of infants with bronchiolitis may have recurrent episodes of wheezing. The most severe acute cases, and the most frequent recurrences, are seen in patients with a positive family history of allergy and in patients with congenital heart disease.[212] Incomplete immunity to respiratory syncytial virus and reexposure to the virus also account for some episodes of recurrence.[350] The more begging question is whether an episode of bronchiolitis may reflect a predisposition to chronic obstructive pulmonary disease later in life. The answer is unknown, although as many as one-third of infants with acute severe bronchiolitis have been found to have recurrent coughing attacks, and as many as 75% have lung function abnormalities, when studied 1 year after the acute episode.[313] Of course these patients were selected by virtue of the severity of their initial episode. In a population with a wider spectrum of acute infection, 57% of 48 children had increased bronchial reactivity when studied 9 or 10 years after admission to hospital with bronchiolitis.[136] Again, these patients' conditions were severe enough to require hospitalization and, therefore, may not reflect those of the vast majority of children with bronchiolitis in infancy. Nonetheless, the likelihood is present that as many as one-third of patients with bronchiolitis and a strong family history of allergic asthma may have recurrent and persistent bronchitis, episodes of wheezing, and asthma.

Prevention

There is at present no adequate prevention for this disease. An attempt to use a killed virus vaccine ended disastrously, as patients appeared to be more sensitive to the ill effects of the viral infection after receiving this product.[138] The prevention of respiratory syncytial virus in the community depends on avoiding contact with infants and children with respiratory infections due to this virus. This is not an easy task, as mentioned above, due to the diverse manifestations of this viral infection in various age groups.

In the hospital setting, respiratory syncytial virus infections spread most commonly by direct and close contact.[139] Hence, patients likely to have respiratory syncytial virus infections should be nursed in a single room or with patients with infections of similar etiology. Careful handwashing and appropriate decontamination of objects in direct contact with the patient seem judicious.

Pneumonia

Epidemiology

Eighty percent of pneumonias in children occur in those under the age of 7 years, with the peak incidence in 2–4-year-olds. Boys are more frequently affected than girls, and viruses and mycoplasma account for the vast majority of these infections. The causes of pneumonia vary with geography, exposure, host factors, and epidemics. For example, tuberculosis is endemic in many countries and influenza A virus accounts for considerable morbidity in epidemic years. Pneumonia is most common in the winter and early spring. In children, this often reflects the prevalence of respiratory syncytial virus, parainfluenza, and/or influenza viruses. Spread of influenza B and other respiratory viruses among children in day-care centers is common.[184a]

Pathogenesis

Pneumonia can occur as part of a generalized (upper and lower respiratory) infection. Concurrent or subsequent infection by a second pathogen may occur in as many as 20% of cases.[246] Most often these are two viruses, a virus and a mycoplasma, or viral infection followed by bacterial pneumonia. The initial infection may disrupt the usual pulmonary defenses, i.e., aerodynamic filtration, cilia, mucus, pulmonary alveolar macrophage, circulating neutrophils and macrophages, lymphocytes, complement, antiproteases, lysozyme, and fibronectin,[241] thus setting the stage for superinfection.[98] The sequence in most cases is as follows: upper respiratory colonization → lower respiratory colonization → bronchopulmonary injury. When bacteria are involved this may be followed by bacteremia; however, there is little evidence to suggest viruses or mycoplasma invade the bloodstream in a similar fashion. Patients with certain underlying conditions are more prone to develop pneumonia during the course of viral respiratory infection. Such conditions include cystic fibrosis, α_{-1}-antitypsin deficiency, the immotile cilia syndrome, immunodeficiencies, and severe debilitating and immunosuppressive diseases and treatments. Recurrent aspiration pneumonia is seen in patients with various neurologic conditions, gastroesophageal reflux, and familial dysautonomia (Riley-Day syndrome).[32] Similarily, mechanical ventilation is an important factor in the pathogenesis of nosocomial colonization and pneumonia.[104]

Pneumonia can also develop after hematogenous seeding of the lung with pathogenic organisms (e.g., *Staphylococcus aureus, Haemophilus influenzae*). Remember that pathogenicity and virulence are partly determined by host characteristics, hence, many opportunists may also cause bloodborne pneumonia in immunocompromised patients (e.g., Legionella, cytomegalovirus, *Candida albicans, Pseudomonas aeruginosa*).[39] *Mycobacterium tuberculosis* is an example of a pathogen that may cause both endobronchial or miliary (hematogenous) pneumonia.

Etiology

The common infectious causes of pneumonia are listed in Table 5–4. Viruses and mycoplasma account for the majority of cases of pneumonia in North America. In one study, over 6000 episodes of childhood pneumonia were prospectively observed over an 11-year period.[242] Approximately 25% were unequivocally due to viruses (respiratory syncytial,

TABLE 5-4. Infectious Causes of Pneumonia

- Viruses
  - Respiratory syncytial
  - Parainfluenza 1, 3, 2
  - Influenza
  - Adenovirus
- Cytomegalovirus[39]
- Epstein-Barr virus[7]
- Herpes simplex[267]
- Mycoplasma
  - *Mycoplasma pneumoniae*
  - *Ureaplasma urealyticum*
- Bacteria
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*
  - *Legionella pneumophila*
  - *Mycobacterium tuberculosis*
  - *Pseudomonas pseudomallei* (Meliodosis)
- Chlamydia
  - *Chlamydia trachomatis*
  - *Chlamydia psittaci*
- Fungi
  - Histoplasma
  - Coccidioides
  - Candida
  - Cryptococcus
- Rickettsia
  - *Coxiella burnetii* (Q fever)
- Parasites
  - *Ascaris lumbricoides*
- Protozoa
  - *Pneumocystis carinii*

parainfluenza viruses 1 and 3, and influenza A) and *Mycoplasma pneumoniae*. Approximately 60% of the pneumonias occurred during the peak prevalence of virus and mycoplasma activity in the community. Pneumonia in the first 3 months of life may be due to Chlamydia, cytomegalovirus, Ureaplasma, or *Pneumocystis carinii*, singly or in combination.[88]

The potential for pulmonary infection exists with almost all microbial pathogens, including common oral flora, such as *Branhamella catarrhalis*.[216] The tracheobronchial tree and lungs are normally sterile. Introduction of microorganisms into these areas can lead to pneumonia if certain other conditions are present. Virulence and quantity of the inoculum and characteristics of the host (such as age and underlying conditions) are major determinants for the development of pneumonia and its outcome.

Unusual exposures may also suggest infrequent causes. Examples include Q fever after contact with sheep, psittacosis (parrots and other birds), tularemia (rabbits), and *Salmonella choleraesuis* infection after contact with pigs.[132]

Let us look at some of the factors. Certain infections are more prevalent in young infants. Pneumonia in the newborn is discussed in Chapter 3. In the first 6 months of life, *Chlamydia trachomatis* is often associated with a chronic afebrile pneumonia. Sometimes these infants have coexisting infection with cytomegalovirus, respiratory syncytial, adenovirus, rhinovirus, or enterovirus. Primary bacterial pneumonias are not very common in this age group, particularly in normal hosts in North American populations. Beyond the first year of life, viruses continue to play a major role in pneumonia, although mycoplasma become more prevalent (Fig. 5-2). When bacterial infections occur, with the exception of tuberculosis,

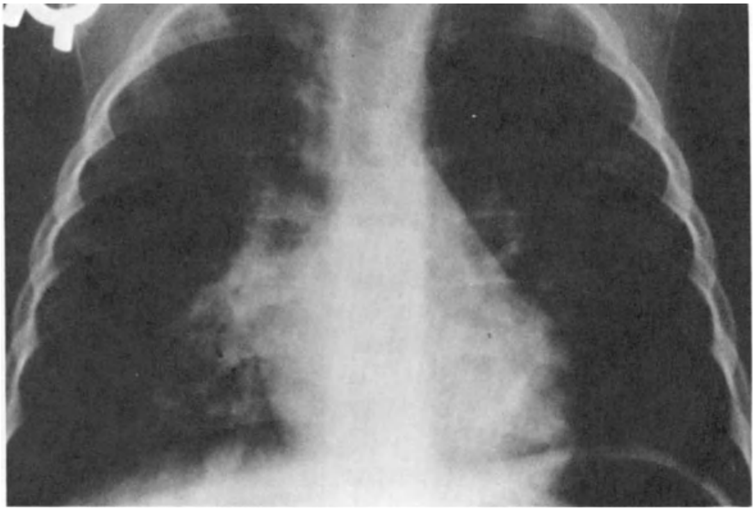

Figure 5–2. Adenovirus pneumonia in a 3-year-old.

the vast majority are due to four major pathogens: *Streptococcus pneumoniae, Haemophilus influenzae,*[13] *Streptococcus pyogenes,* and *Staphylococcus aureus.* The morbidity associated with staphylococcal[61] and streptococcal[236] pneumonia in infants and children is still considerable.

In school-age children and adolescents, *Mycoplasma pneumoniae* is a major cause of pneumonia; however, Haemophilus pneumonia may be seen in adolescents.[167] It is estimated that up to 20% of all cases of pneumonia in children over the age of 5 years are due to Mycoplasma. Pneumonia in patients with infectious mononucleosis may be due to *Mycoplasma pneumoniae* or to Epstein-Barr virus.[7]

Other etiologies are important in pneumonia in abnormal hosts. For example, immunodeficient patients are prone to pneumonia due to other viruses (e.g., herpes group viruses in organ transplant recipients), fungi, and protozoa (e.g., *Pneumocystis carinii*). Children with malignancies and neutropenia (due to bone-marrow relapse or chemotherapy) are highly susceptible to gram-negative enteric pneumonia, while the characteristic bacterial flora associated with pneumonia in cystic fibrosis are *Staphylococcus aureus* and/or *Pseudomonas aeruginosa. Haemophilus influenzae* may also be present. Meningococcal pneumonia has been reported in normal and abnormal hosts[154] and can serve as a source of nosocomial spread.[272]

The microbial etiologies of pneumonia in patients with recurrent aspiration due to neurogenic or anatomic factors are diverse and often reflect colonization of the subglottic area with oral and upper respiratory flora. In these circumstances, pneumonia reflects the inflammatory responses to both microbes and irritating secretions. Similarly, pneumonia associated with certain parasitic infections (e.g., *Ascaris lumbricoides*) reflects the presence of the parasite and a marked host hypersensitivity response.

This is characterized by local and peripheral eosinophil responses in ascariasis and by local granulomatous inflammation in pulmonary tuberculosis.

Clinical Manifestations

Although fever is an important sign of pneumonia, it is nonspecific. Tachypnea; cough; labored respiration; and intercostal, subcostal, or suprasternal indrawing are more specific signs of pulmonary disease. Patients with these signs often have generalized malaise, irritability, anorexia, and fatigue. As a rule, the younger the patient, the more difficult it is to discern the specific signs of pulmonary infection. Abnormally rapid sleeping respiratory rates may be the only clues to the presence of pulmonary inflammation in infants. These measurements can be used not only for the diagnosis of the condition, but also as a guideline to the presence of hypoxemia, carbon dioxide retention, or ventilatory obstruction. The sudden onset of fever and pleural and/or abdominal pain may characterize pneumococcal pneumonia. In fact, in some cases the abdominal pain is so severe that the condition is occasionally misdiagnosed as appendicitis.

Other clinical signs are detected in the physical examination and include the presence of rales, bronchial breathing, decreased breath sounds, and increased dullness. Again, the younger the patient, the more difficult it is to elicit these signs. The presence of rash, wheezing, chills, nausea, and vomiting is rarely specific but sometimes can suggest an etiology. For example, gastrointestinal symptoms are common at the beginning of Legionella pneumonia, vomiting after a paroxysmal cough attack due to pertussis, and a typical rash with varicella pneumonia. Neurologic signs (Reye-like syndrome) may also be present in some patients with adenovirus pneumonia.[194] These are just a few examples of clinical clues that may suggest the etiologic diagnosis of pneumonia. Others are given in Table 5–5.

The clinical manifestations of infections due to lower respiratory pathogens are extremely diverse. An excellent example is provided by influenza, where type A virus causes most severe pneumonias,[125] type B less so,[15] and type C rarely.[89] Mild effects of influenza include liver function abnormalities, estimated to occur in approximately 3% of infected patients.[237] Rarely this may progress to Reye syndrome. Overall, the morbidity and mortality rates associated with influenza are greatest during years when epidemics occur.[124]

Diagnosis

The recent history can provide major clues to the diagnosis. Examples include the unimmunized child who is exposed to a baby-sitter with pertussis, or the patient exposed to an aunt with recently diagnosed

Table 5–5. Clinical Clues to the Cause of Pneumonia

Agent	*Clue*
Viruses	
Respiratory syncytial	Wheezing
Parainfluenza	Laryngitis (croupy cough)
Influenza	Ongoing epidemic/severe myalgia
Adenovirus	Conjunctivitis
Rhinovirus	Common cold signs
Varicella	Skin vesicles
Coxsackie	Skin vesicles/mucous membrane ulcers/myocarditis
Cytomegalovirus	Thrombocytopenia/mononucleosis syndrome
Bacteria	
Staphylococcus aureus	Skin or extrapulmonary abscesses
Streptococcus group B	Hypotension/respiratory distress syndrome in full term
Streptococcus group A	Palatal petechiae
Meningococcus	Skin petechiae
Mycobacterium tuberculosis	Exposure/travel
Bordetella pertussis	Paroxysmal cough/whoop
Other	
Chlamydia trachomatis infection	Afebrile/staccato cough/ conjunctivitis/maternal genitourinary infection
Cystic fibrosis	Pseudomonas ± *Staphylococcus aureus* in respiratory secretions
Coccidioidomycosis	Exposure/travel
Psittacosis	Exposure to sick bird

tuberculosis. Less obvious might be contacts with conjunctivitis or pleurodynia, signs of viral infections that can also manifest as pneumonia. Epidemiologic information is also very useful and often suggests the cause of pneumonia may be coccidiodomycosis or tuberculosis in certain areas, or respiratory syncytial, influenza, or group A *Streptococcus pyogenes* infection during peak activity of these agents in the community.

With those historical and clinical features in mind, the clinician is left with a presumptive diagnosis of pneumonia and some guide to the cause in many infants and children. All cases of pneumonia should be confirmed by radiography. This is particularly important in younger patients in whom signs of empyema, pneumatocele, atelectasis, foreign body, congenital anomalies, etc. may be extremely difficult to detect clinically. Many of the radiographic features mentioned may also provide clues to the etiology (Table 5–6). There are overlaps, however, as illustrated by either bronchopneumonia[166] or lobar consolidation with adenovirus pneumonia[199] and diffuse bronchopneumonia with tuberculosis.

If bacterial pneumonia is suspected and, therefore, antibiotic therapy is considered, blood and appropriate respiratory cultures should be obtained. What are appropriate respiratory cultures? This oft-debated question is still unresolved. The gram stain of expectorated sputum is still one of the most cost-effective tests for the diagnosis of community-acquired pneumonia.[38] In patients who are old enough to provide an adequate specimen (usually over 8 years of age), expectorated sputum should be examined for the presence of cells and microorganisms. Specimens with less than 25 epithelial cells per low-power field (100 × magnification) are usually appropriate. The presence of polymorphonuclear leukocytes or alveolar macrophages helps confirm the impression that this specimen emanates from the lower respiratory tract and that the resultant microbiology will be relevant to the cause of the pneumonia. The history and clinical features should be used to define the procedures carried out on this material.[19] For example, an acid-fast stain is appropriate for patients suspected of having tuberculosis and a wet smear can be used to look for coccidioides or blastomyces. The presence of eosinophils may suggest a diagnosis of allergy; mononuclear cells are often associated with viral infections.

If the patient is not able to expectorate sputum, what can we do? The nasopharyngeal or throat swab is easiest, but the least likely to provide a clue to the diagnosis of bacterial pneumonia. Finding a respiratory virus, *Mycoplasma pneumoniae,* or Chlamydia in these sites is diagnostic,

TABLE 5–6. Radiologic Clues to the Etiology of Pneumonia

Sign	*Etiology*
Diffuse bronchopneumonia with hyperaeration	Respiratory syncytial virus
Lobar consolidation	Pneumococcus Haemophilus[121]
Upper lobe involvement	Cystic fibrosis Tuberculosis
Hilar adenopathy	Tuberculosis Histoplasmosis (lymphoma)
Pneumatocele	*Staphylococccus aureus* occasionally gram negative bacteria including Haemophilus,[65] Pseudomonas, Klebsiella, Pneumococcus,[5] Kerosene ingestion[5]
Pleural fluid	Staphylococcus Haemophilus[121] Tuberculosis can also be viral or mycoplasma
Uneven diaphragms with or without atelectasis	Foreign body

since these are not normal flora. Occasionally, one can find group A Streptococcus, Nocardia, or other rare pathogens in the upper respiratory tract that may have significance. However, the presence of *S. pneumoniae, Staphylococcus aureus,* or Haemophilus in the upper respiratory tract is usually of no use in defining the cause of lower respiratory infections.

Respiratory secretions can often be obtained from young infants by aspiration of tracheal material under direct laryngoscopic examination. Endotracheal or nasotracheal aspiration can also be employed. In older patients, transtracheal aspiration may be useful in the diagnosis of pneumonia. These procedures are recommended for selected patients with severe or complicated illness, atypical courses, or poor responses to initial therapy.

When pneumonia persists or progresses, or unusual pathogens or foreign bodies are suspected, bronchoscopy may also be useful. This procedure does introduce some contaminants, a factor that should be kept in mind when interpreting culture results. Quantitative bacteriology and protected catheter cultures are useful.[263] Percutaneous lung aspiration and lung biopsy specimens are generally reserved for particular hosts and severe infections.[201] These are discussed in reference to pneumonia in the newborn although similar principles apply in older patients (see Chapter 3).

The patient with an indwelling endotracheal tube or tracheotomy presents a special problem. In most circumstances, the trachea acquires respiratory flora within 24 h of intubation or tracheotomy. In cases of prolonged pneumonia with intubation and respiratory support, baseline studies should include examination of the cytology and microbiology of endotracheal specimens. Shifts in the cell population to largely neutrophils, and in the microbiology toward a predominant pathogen, should be used to guide management, along with clinical and radiographic findings.

A blood culture should be obtained in all patients suspected of having bacterial pneumonitis. Bacteremia is present in approximately one-third of cases of pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae.* This percentage may be greater if the pathogenesis of pneumonia involves hematogenous spread from an extrapulmonary focus. Capsular polysaccharide antigens may also be detected in the urine of patients with pneumonia.[336] Hence, a urine examination for pneumococcal and Haemophilus antigen should be done in patients in whom these diagnoses are suspected. If empyema is present, thoracentesis should be performed before institution of antibiotic therapy and appropriate stains, cultures, and antigen studies performed.

In summary, the diagnosis of pneumonia is a complex one, derived from historical, clinical, and microbiologic evidence. Not all cases require all tests. The patient with bronchopneumonia or viral pneumonia need not have all of these studies for bacterial causes. This is acceptable as

TABLE 5-7. Differential Diagnosis of Pneumonia in Infancy and Childhood

Thymic shadow in newborn
Aspiration (e.g., gastroesophageal reflux, tracheoesophageal fistula, foreign body)
Hydrocarbon poisoning (e.g., kerosene)
Congenital pulmonary anomalies (e.g., sequestered lobe)
Congenital cardiovascular anomaly (e.g., vascular ring)
Hypersensitivity pneumonitis
Drug (e.g., nitrofurantoin) or radiation pneumonia
Postinflammatory pseudotumor
Sarcoidosis
Histiocytosis
Leukemia
Rheumatoid arthritis

Recurrent pneumonia

Foreign body
Gastroesophageal reflux
Cystic fibrosis
Immotile-cilia syndrome
Immunodeficiency
Congenital lung anomaly

long as it is also understood that such patients do not require antibiotic therapy.

Mycoplasma pneumoniae should be confirmed by appropriate serology (complement fixation). Mycoplasma cultures are not readily available and are too slow and insensitive for routine clinical use. An early clue to the diagnosis may be provided by an elevated serum concentration of cold agglutinins; however, these may also be associated with adenovirus, coxsackievirus, Epstein-Barr virus, and other causes of respiratory infection.

Differential Diagnosis

Pneumonia may be confused with several other conditions that lead to inflammation of the lungs or pulmonary consolidation (Table 5-7). In some situations, the pneumonia may be recurrent and may reflect underlying conditions that require additional investigation and treatment.[171] The same principles apply as those discussed in reference to frequent respiratory infections (Chapter 4). If an immune deficiency is suspected, every effort should be made to establish the exact etiologic diagnosis with each episode of pneumonia. In such cases, recurrent staphylococcal pneumonia may suggest a defect in phagocytosis or intracellular killing of the specific organism, whereas the presence of Serratia, Nocardia or Aspergillus may suggest chronic granulomatous disease. Common respiratory viruses and mycoplasma are associated with exacerbations of asthma and other reactive airway diseases. Nonspecific microbiologic findings may indicate recurrent aspiration, tracheoesophageal fistula, or presence of a foreign body. Chronic cough may be a manifestation of asthma rather than of pneumonia or bronchitis.[143] Other noninfectious causes of chronic cough include smoking, neoplasms, and psychogenic conditions.[101]

Treatment

Once an etiologic diagnosis is made, the treatment is reasonably straightforward. Hence treatment of infections due to *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and penicillin-sensitive *Staphylococcus aureus* consists of penicillin for approximately 1 week in normal hosts. Therapies for the four common bacterial causes of pneumonia in infancy and childhood are summarized in Table 5-8.

Antimicrobial treatment of other causes of pneumonia depends on microbiologic information about identification and susceptibility of the pathogen (see subsequent sections in this chapter). Characteristics of the host and pharmacokinetics of antibiotics, such as their penetration into the sputum and bronchial tissues,[298] need to be considered in choosing appropriate drugs, routes, and durations of therapy.

What about viral pneumonias? Influenza is much more likely to be

TABLE 5–8. Antibiotic Therapy of Common Bacterial Pneumonias in Infants and Children

Etiology	*Drug*	*Dose (per kg/day)*	*Duration*[a]	*Route*
Streptococcus pneumoniae	Penicillin	50,000–250,000 units	5– 7 days	IV/Oral
Streptococcus pyogenes				
H. influenzae Ampicillin-sensitive	Ampicillin	100–200 mg	7–10 days	IV
	or			
	amoxicillin	50–100 mg	7–10 days	Oral
Ampicillin-resistant	Moxalactam	100 mg	7–10 days	IV
Staphylococcus aureus penicillin-resistant	Oxacillin	100–200 mg	10–14 days	IV
	or			
	dicloxacillin	50–100 mg	10–14 days	Oral

[a] Duration may be prolonged with complications

superinfected with bacteria than adenovirus. Although viral pneumonias may predispose the host to bacterial superinfection, there is little value in trying to prevent this by means of antibiotic therapy. It is much more useful to observe the patients for signs of secondary infection and institute appropriate management at an early stage. These signs include persistent or renewed temperature elevation, chills, malaise, persistent anorexia, and the development of purulent sputum in the older patient. Purulent or copious sputum alone should not be used to imply the presence of secondary bacterial infection. Associated fever and toxicity are meaningful.

Of the primary pneumonias, only influenza A can be treated specifically. Both amantadine[364] and aerosolized ribavirin[186] are effective. Amantadine hydrochloride 5 mg/kg/day orally (maximum 150 mg) can shorten the duration and severity of infection.[44] The earlier it is given in the course of illness, the greater the effect. In fact, the drug can be used to prevent influenza A infection in susceptible contacts. Unfortunately, it has no effect on influenza B or other respiratory viruses. Vidarabine or acyclovir can be used to treat herpes simplex or varicella pneumonia, usually present in specific hosts or as part of a disseminated infection. The dose of vidarabine and acyclovir is 15 mg/kg/day and 30 mg/kg/day, respectively. Both drugs are administered parenterally and usually for a 7–10-day course.

Mycoplasma pneumoniae infection is treated effectively by erythromycin 40 mg/kg/day divided q 6 h administered orally. Tetracycline 50 mg/kg/day is useful in children above the age of 8 years. Fever generally decreases within 2 or 3 days and the patient feels well 4 or 5 days after institution of therapy. Cough may be prolonged, and *Mycoplasma pneumoniae* may not be eradicated easily by antimicrobial therapy. This should be kept in mind when considering contagiousness.

Cough is an important defense mechanism which functions by improving the clearance of infected secretions.[20] Indications for cough suppression include disruption of sleep and eating habits to the detriment of the host. Cough preparations should be prescribed cautiously and are rarely indicated in infants under 1 year who are particularly susceptible to respiratory depression and obstruction of small airways by retained secretions.[287] Chest physiotherapy may be useful in patients with large amounts of secretions, particularly young infants and in those with lung abscesses, foreign bodies, and consolidated disease. Oxygen, nutrition, hydration, and correction of underlying host abnormalities are important components in the therapy of pneumonia. The indications for each should be clearly defined and their use controlled by objective parameters.

Prevention

The principles for prevention of pneumonia are similar to those applicable to other respiratory infections. These depend on knowledge of the pathogenesis (e.g., pneumonia may often develop secondary to an upper respiratory infection), etiology, epidemiology (e.g., influenza A), and shedding patterns of respiratory pathogens. For example, influenza, respiratory syncytial, and parainfluenza viruses are generally shed in greatest quantity during the first week of illness.[115] Direct contact plays a prominent role in spread of many upper respiratory infections, and nasal and conjunctival mucosal sites are frequently the initial sites of colonization. Influenza virus survives for as long as 2 days on hard environmental surfaces.[24] Respiratory (aerosol) spread seems important for influenza, adenovirus, tuberculosis, and histoplasmosis. Vaccination and amantadine[83] can be used to prevent influenza pneumonia, and bacillus Calmette-Guerin (BCG) for tuberculosis control. In hospital, methods of achieving respiratory tract isolation, including the wearing of masks, are most useful in controlling agents spread by aerosol. Careful handwashing is critical for the isolation of patients with these and other causes of pneumonia. A recent hospital outbreak of adenovirus type 7 infection illustrates the potential gravity of such spread.[314] Four of six infected children died.

Complications

Early complications of pneumonia are infrequent in childhood but can be life-threatening. Severe overwhelming infection[367] and fatal pneumonia[182] have been reported due to adenovirus in both normal and immunocompromised patients. Other complications include pneumothorax, massive pleural empyema, pneumatocele formation, bacteremia with subsequent extrapulmonary infectious complications, and effects of ventilatory obstruction and severe hypoxemia. These problems are best monitored by prospectively following the sleeping or resting respiratory rate, pulse, and general clinical condition of the patient. This can be done at home or in hospital, depending on the reliability of observers. Regardless of the antibiotic and general supportive therapy provided, observation is critical in the first few days after the diagnosis of pneumonia.

Longer term complications of pneumonia are, fortunately, rare. In the vast majority of children, the chest radiograph returns to normal within 3 months, although as many as 20% will still have abnormal X-rays 3–4 weeks after diagnosis.[134] Thus, a normal chest X-ray in the third month of convalescence will help exclude serious underlying diseases and rare complications of pneumonia. The latter include congenital anomalies, obstructive bronchiolitis with hyperlucent lung,[301] bronchiectasis, postinflammatory pseudotumor,[50] and persistent atelectasis. Remember, asthma is a common cause of persistent or recurrent pneumonia.[102] The role of pneumonia acquired in infancy or childhood in the pathogenesis of adult pulmonary disease is unclear. It is conceivable that viral and Mycoplasma pneumonias may predispose certain genetically prone hosts to chronic bronchitis and obstructive pulmonary disease as adults. Smoking, air pollutants, and other factors no doubt play roles as well.

Empyema

Epidemiology

Empyema in infancy and childhood is much less common in developed countries than in developing areas. This correlates with the incidence of life-threatening staphylococcal pneumonia and malnutrition. In societies where both are rampant, empyema is still a serious problem. In such situations, empyema is most commonly seen in the first 2 years of life and requires aggressive therapy. Early and complete drainage of pus and nutritional management are critical to recovery.

In developed countries, empyema is rare in newborns and uncommon throughout infancy and childhood. It is still most frequently seen in the first 2 years of life, and most commonly associated with previous episodes of pneumonia. The condition is unilateral in > 90% of cases. Normally, the pleural space contains less than a milliliter of fluid which has a protein concentration of approximately 1 mg/ml.[275]

Pathogenesis

The vast majority of cases of pleural empyema are noted in the acute stage of staphylococcal pneumonia or in the acute or convalescent stages of pneumonia due to *Streptococcus pneumoniae, Haemophilus influenzae,* and a variety of other bacterial pathogens.[72] Rarely, two pathogens, such as influenza and *Staphylococcus aureus,* may be recovered from pleural empyema fluid.[221] The propensity of these organisms to infect the pleural space is probably related to lymphatic obstruction which may be seen as a component of the original episode of pneumonia. Relevant host defense mechanisms include pleural macrophages and inflammatory fluids, and cells attracted to the area by infecting microorganisms. This is a double-edged sword, as elastase and other polymorphonuclear leukocyte enzymes have recently been demonstrated to be anticomplementary in pleural fluid.[320] This may decrease the capacity of cells to phagocytose bacteria.

In other situations, the pathogenesis of pleural empyema in children is clearly related to trauma, surgery, the presence of a foreign body, or associated with lung abscess. It is occasionally seen after mediastinal radiation or after segmental or lobar pneumonectomy.[2] Patients with staphylococcal empyema should be screened for the presence of cystic fibrosis as an underlying condition.[325] Any patient with repeated bacterial empyemas should be examined for immunodeficiencies. In contrast with the situation in young children, in the older patient pleural empyema is most commonly associated with chronic obstructive pulmonary disease and aspiration syndromes associated with a variety of underlying causes, including alcoholism, drug addiction, and other conditions manifest by poor pharyngoesophageal coordination.

Etiology (Table 5-9)

Common lower respiratory pathogens such as *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* are causes of bacterial empyema in children.[66] Tuberculosis is still prevalent in many parts of the world,[103] and histoplasmosis may also be causative. In cases of empyema associated with aspiration, anaerobic organisms may be present, including *Clostridium perfringens*[290] and *Eikenella corrodens.*[312] The presence of foul-smelling pus and/or gas in the pleural fluid should suggest this etiology.[109] Trauma and surgery are common predisposing factors for clostridial empyema, but the condition is occasionally seen in normal subjects.[192]

It is surprising how often other common causes of pleural empyema are not considered. Tuberculosis should be included in this group, but so should *Mycoplasma pneumoniae,* which may be associated with a poly-

TABLE 5-9. Etiology of Pleural Empyema

- Bacteria
  - *Staphylococcus aureus*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*
  - *Haemophilus influenzae*
  - *Haemophilus parainfluenzae*
  - Anaerobes (streptococci, Bacteroides, clostridia)
  - *Mycobacterium tuberculosis*
  - *Pasteurella multocida*[127]
  - *Yersinia enterocolitica*[69]
- Viruses
  - Adeno
  - Coxsackie
  - Influenza
- Combined
  - *Staphylococcus aureus* + influenza A virus
- Fungi
  - *Histoplasma capsulatum*
  - *Candida albicans*
  - Aspergillus[252]
- Others
  - *Mycoplasma pneumoniae*
  - *Chlamydia*
  - Parasites[177]

morphonuclear response in the pleural fluid. Adenovirus is not uncommonly associated with pleural fluid collections, and, in the very early stage, the predominant cells may be polymorphonuclear. Generally, other viral infections are associated with lymphocytic pleural effusions.

Clinical Manifestations

The clinical features that suggest the presence of empyema are rarely appreciated in the pediatric age group. Older patients complain of chest pain and fullness and may actually guard the affected side. Examination of the chest most specifically reveals decreased breath sounds and dullness to percussion. Less than 20% of children report chest pain and less than 15% have hemoptysis. Most do have fever, tachypnea, and tachycardia. Some report dyspnea and cough, the latter being more common in those in whom underlying pneumonia precedes the development of empyema. Fever, mild tachypnea, and cough may be present for 3–6 weeks before the diagnosis of empyema is appreciated in some cases. Most patients, however, who have empyema associated with common lower respiratory bacterial infections appear acutely ill, and are very irritable. Remember that patients receiving corticosteroids and those who are severely malnourished or otherwise debilitated by other underlying diseases may have few localizing signs.[276]

Diagnosis (Fig. 5-3)

Chest X-ray and thoracentesis are the major diagnostic tools in such cases. The clinician is often astonished to see pleural fluid on the X-ray of the patient with few clinical signs. In some situations, lateral decubitus views are required.[339] As little as 10 ml of fluid can be appreciated by this method. This procedure should be included in the examination of the chest in patients with prolonged fever associated with pneumonia, and in those complaining of chest pain, fullness, and persistent dyspnea. After all, making the diagnosis of pleural effusion offers a highly specific fluid for diagnosis.

The next step is percutaneous needle aspiration to obtain fluid for culture and other studies. Bacterial cultures of empyema are often positive despite prior antibiotic therapy, but special cultures may be required (e.g., hypertonic media, penicillinase, antibiotic removal devices). Blood cultures are indicated (do at least one after the thoracentesis, as transient bacteremia may be induced by the procedure) as are tests for Haemophilus and pneumococcus (and group B Streptococcus in newborns) antigens in the pleural fluid and urine.[195] Patients suspected of having meningococcal pneumonia, although rare, may also be diagnosed by finding specific polysaccharide capsular antigen in the pleural fluid, urine, or, rarely, in the serum.

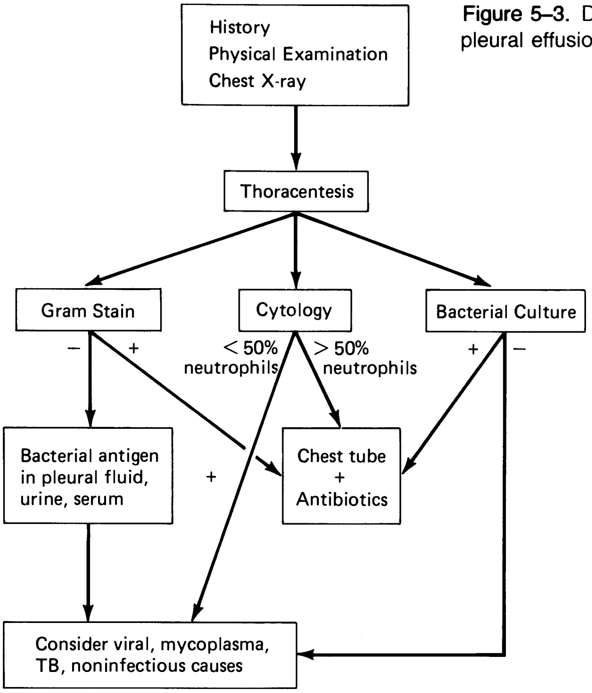
History
Physical Examination
Chest X-ray
Thoracentesis
Gram Stain
Cytology
Bacterial Culture
−
+
< 50% neutrophils
> 50% neutrophils
+
−
Bacterial antigen in pleural fluid, urine, serum
+
Chest tube + Antibiotics
Consider viral, mycoplasma, TB, noninfectious causes

Figure 5–3. Diagnosis and management of pleural effusion.

The definition of pleural empyema and its distinction from pleural effusion is very arbitrary. Various criteria, including the grossly purulent appearance of the fluid, the presence of > 10,000 polymorphonuclear leukocytes/mm^3, and a predominance ($\geq$ 70%) of neutrophils among these cells have been used to define empyema. Other criteria include an acid pH, an increased protein concentration, and/or a positive gram stain. Whatever the definitions used, the importance lies in the description of the etiology and pathogenesis. Hence, a positive gram stain, the presence of bacterial antigens, and positive cultures are useful. A low sugar concentration in the pleural fluid is commonly present in bacterial empyema, but is also present in mycobacterial empyema, and pleural effusion associated with tumors and rheumatoid arthritis.[49] The patients with the greatest cellular inflammatory response and the most tissue damage will have the highest pleural fluid lactic acid concentrations,[62] lactic acid dehydrogenase enzyme levels, and the lowest pH. Although it has been proposed that the pH can be correlated with the severity of the disease, this correlation is crude and should not be relied upon as the sole diagnostic criterion for defining the etiology or the therapeutic approach.[128] In some instances, where the differentiation of lung abscesses from pleural effusions may be difficult, ultrasound and computerized tomography can be used. These procedures are also useful in defining the extent and loculation of such fluids.

The pleural fluid from patients in whom tuberculosis is suspected should be cultured for mycobacteria, although this test is negative in as many as 70% of cases. The sensitivity of the culture method can be increased by using large volumes of pleural fluid and by preparing multiple cultures. Much more important is the use of pleural biopsy. Cultures may be positive in as many as three-quarters of pleural biopsy specimens and histology can indicate a granulomatous disease in 50–80% of cases. Remember that pleural biopsy should be performed only when fluid is present in the pleural space in order to avoid serious pneumothorax and hemorrhage. A Mantoux tuberculin skin test is important, but may be falsely negative in the face of debilitation, and is less specific in endemic populations.

Although rare, patients can have right-sided pleural effusions associated with hepatic amebiasis. In such cases, the fluid is often bloody or brownish-red. Amoeba and liver tissue fragments may be present in the fluid as well.

Differential Diagnosis

Fluid in the pleural space can be present in association with a variety of underlying problems (Table 5–10). In the newborn, chylothorax is common. In the older patient, a variety of associations have been described. Although the differential diagnosis is wide, many of these conditions are rare in the pediatric population. In the presence of eosinophils, hypersensitivity to drugs, parasites, and foreign bodies should be added to the differential diagnosis.[275]

Other laboratory tests are also useful when some of the noninfectious diagnoses are considered. For example, low concentrations of complement are seen in the pleural fluid of patients with rheumatoid arthritis and systemic lupus erythematosus. In these patients rheumatoid factor and lupus erythematosus cells may also be present in these fluids.

Therapy

Two major types of infectious empyemas are encountered. In one, the empyema is associated with acute pneumonia and the patient is severely toxic. Debilitated patients with staphylococcal pneumonia best exemplify this presentation, although it is sometimes also seen in association with pneumococcal, streptococcal, and Haemophilus pneumonia. The fluid in such cases is often thin and full of bacteria and neutrophils, and chest pain and toxicity may be prominent. In these situations, closed chest tube drainage should be instituted immediately after thoracentesis has confirmed the presence of pus.[3] The advantages include relief of pain, rapid and continuous removal of bacteria with their associated toxins, and

TABLE 5-10. Noninfectious Pleural Effusion: Differential Diagnosis

- Newborn
  - Chylothorax
  - Congenital pleural effusion (usually bilateral)
- Others
  - Congestive heart failure
  - Myxedema
  - Pancreatitis
  - Nephrosis
  - Cirrhosis
  - Constrictive pericarditis
  - Rheumatoid arthritis
  - Polyarteritis nodosa
  - Systemic lupus erythematosus
  - Sardoidosis
  - Hemothorax
  - Infectious mononucleosis
  - Pulmonary infarction
  - Lymphoma
  - Mediastinal irradiation
  - Foreign body
  - Ovarian cyst
  - Tumor
  - Hypersensitivity (drug, parasite)
  - Subdiaphragmatic abscess

removal of polymorphonuclear leukocytes, which elaborate a variety of destructive enzymes as well. The approach may be rewarded by shortened hospitalization and decreased morbidity. In patients in whom malnutrition and other underlying diseases are present, drainage may be life-saving.

Drainage is critical for diagnosis and in order to reduce morbidity. It is also useful because of the predisposition of these patients to develop pneumothorax. This can occasionally be bilateral or under tension, both life-threatening events. When drainage is used, the largest tolerable intercostal drain should be inserted. It should have many holes and be connected to underwater seal and suction. If the tube becomes clogged by thickened secretions, it should be replaced. When the tube no longer drains fluid, it should be removed. There is no need to shorten the tube, since development of sinus tracts and fistulae is not reported with pleural empyema in pediatric patients. Their presence should suggest actinomycosis, untreated tuberculosis, or malignancy.

One exception to this is the presence of tuberculous empyema; chest tube drainage and repeated thoracentesis are seldom useful and, in fact, may be associated with poor healing and sinus tract formation.

The second type of empyema seen more commonly in developed countries is of more insidious onset. It is generally noted 5 or more days after the diagnosis of pneumonia and is characterized by persistent fever and moderate malaise in the young patient. The fluid in such cases is thicker, loculation may be present, and bacteria may no longer be viable. Some of these cases may have thin fluid containing predominantly mononuclear cells. This is seen in the convalescent stage of pneumococcal pneumonia or secondary to viral or mycoplasma infection. Here the debate about therapy rages, since it is unclear when drainage is indicated, and if repeated thoracentesis are preferable to closed chest tube drainage. Unfortunately, there are no controlled studies to fall back upon.

The route of antimicrobial therapy is usually not critical, since the penetration of most drugs into the pleural space is good, generally of the order of 50% or greater of serum concentrations.[324] These concentrations are usually achieved within 3–12 h of the initiation of the first dose of therapy. Thus patients should receive appropriate parenteral antibiotics or oral dicloxacillin 100 mg/kg/day for staphylococcal empyema, or amoxicillin in the same dosage for Haemophilus empyema.[79] Penicillin 200,000 units/kg/day is useful therapy for streptococcal empyema.

A small number of patients, seen late in the evolution of their disease, may require open drainage. This is indicated if closed test tube drainage is ineffective and large loculated empyema fluids are present in a highly symptomatic patient. However, with proper attention to nutrition and stabilization of any underlying disease, and in normal children, this procedure and decortication are rarely necessary.

Viral and mycoplasmal pleural effusions resolve spontaneously over 1–2 weeks although pleural thickening may be evident radiographically for longer periods.

Prognosis

The majority of patients resolve the acute signs of empyema within 7–10 days. Fever is usually slow to disappear, often lasting 5–7 days. Appetite and other generalized signs slowly normalize during this period of time as well. Complications of pleural empyema in infants and children are uncommon. This is in marked contrast to experience in adults, where underlying debilitating disease and aspiration are so frequently associated with pleural empyema.[337] In children, mortality rates are $< 5\%$[53] and most of these are seen in patients with underlying disease and/or severe malnutrition.

One grave early complication is pneumothorax. As mentioned above, this can be life-threatening in certain situations. As many as 46% of cases of staphylococcal empyema, and 28% of all empyemas in children, have been associated with the development of pneumothorax.[53]

Rarely, an empyema may present several weeks to months after an acute febrile respiratory illness. The original illness probably represented a pneumonia that resolved without therapy. The empyema that presents late can become evident in several ways. One of these, a rare feature in modern times, is the protrusion of an intercostal wall mass, called "empyema necessitatis." I have seen this in an adult after pneumococcal pneumonia,[218] and once in a child with Wiskott-Aldrich syndrome. In both cases, *Streptococcus pneumoniae* was the etiologic agent.

The long-term prognosis for children with bacterial empyema is excellent, despite the fact that X-ray changes may be seen for 6 months or longer in some of these children. This is usually due to thickened pleura, but is rarely associated with clinical signs. The only indication for decortication is persistence of marked respiratory dysfunction, chest pain, or fever. Use of ultrasound and computerized tomography may demonstrate areas of loculated fluid that can be evacuated before total decortication is considered. In most patients, pulmonary function tests revert to normal within a year after the initial acute disease is resolved.[280]

Lung Abscess

Pathogenesis/Etiology

Lung abscesses generally develop as complications of bacterial pneumonia, impacted foreign bodies, aspiration, and in preexisting bronchogenic cysts. Patients with seizures, aspiration during dental work,[310] immunologic deficiencies, and mental retardation, as well as comatose infants and children, are particularly prone to this complication. Since staphylococcal pneumonia is a known complication of influenza and malnutrition, it is not surprising to see lung abscesses with either or both of the predisposing conditions. In the newborn, lung abscess may develop as a complication of group B streptococcal or gram-negative pneumonia (especially *E. coli* and Klebsiella). Primary lung abscess (lung abscess without defined cause or association) is probably a sequel to inapparent pneumonitis and/or radiolucent or degradable foreign body aspiration.[341]

This is a rare condition, with only 14 cases reported over a 19-year period in a recent series from a large children's hospital.[12] These abscesses involve primarily the right lung, again suggesting that aspiration often plays a role in its pathogenesis. The predominant etiologic agents in the newborn are mentioned above, and in the older child *Staphylococcus aureus* is most frequently found, although anaerobic and aerobic streptococci and other anaerobes may also be present. Tuberculosis, histoplasmosis, coccidiomycosis, and echinococcosis[178] should also be included in the etiology of lung abscesses, as should many cases of staphylococcal pneumonia.

Clinical Presentation/Diagnosis

There are rarely signs to suggest the presence of lung abscess in children. Aside from the predisposing factors mentioned above, prolonged fever and cough may be the only clues. The chest X-ray is essential to the diagnosis. In the series mentioned above, four of 14 patients had no clinical signs suggestive of localized disease.[12] In certain cases, contrast-enhanced computerized tomography may be useful in the differentiation of lung abscess from pneumatocele or lung cysts and in the accurate localization and anatomic description of the lesion.[222] Confusion with pulmonary emboli and neoplasms is rarely encountered in the pediatric age group, although commonly included in the differential diagnosis of lung abscess in the adult patient.

Treatment

The treatment of lung abscess is unstandardized and supported by very little controlled data. Since the predominant pathogens in newborns are gram-negative bacilli and group B Streptococcus, antibiotic therapy for patients in this age group should be initially directed against these agents. Since therapy may have to be prolonged for 2–8 weeks, every effort should be made to obtain material from the abscess in the newborn before the initiation of antibiotic therapy. Remember, the newborn is a relatively immunocompromised host and drainage may also be required. This can be accomplished through bronchoscopy, percutaneous needle aspiration, or thoracotomy. Any associated empyema needs to be drained by a large chest tube as early as possible.

Primary lung abscess in the older infant and child seems more responsive to medical management. Antibiotics directed against *Staphylococcus aureus,* such as oxacillin or penicillin, can often be used. The oral route is probably as effective as intravenous therapy, although studies documenting this approach in children are lacking. The use of clindamycin has been proposed in the adult patient with fetid sputum, since this sign is usually associated with anaerobic infection.[205] However, anaerobic lung infection with the symptom of foul-smelling sputum is rare in childhood. It is expected mostly in the patient with previous dental work and aspiration of oropharyngeal flora.[204]

Defervescence within 7–10 days after initiation of therapy is usual for lung abscess in infancy and childhood. Patients who are very ill, and those responding slowly to medical therapy, should be considered for bronchoscopy and drainage procedures. Bronchoscopy is indicated early in patients in whom foreign body aspiration is suspected. Surgery may be the definitive procedure in patients with bronchogenic cyst or other predisposing congenital anomalies of the lung, and in those with specific infections, such as echinococcus.

Prognosis

The long-term prognosis in primary lung abscess of childhood seems benign. Despite persistent radiographic changes up to 5 years after the initial diagnosis, most of these children are asymptomatic and their lesions slowly resolve.[12] Thus the presence of thin-walled cysts or parenchymal scars should not be an indication for surgery or other therapies in the asymptomatic patient recovering from lung abscess. A thorough investigation for immunodeficiency, foreign body, and other congenital anomalies and conditions that favor aspiration should be carried out in all patients. This is a rare condition, but its pathogenesis and etiology need to be carefully defined in each case. Although the vast majority of children do well, there were two deaths in 13 patients reported in a recent review.[224]

There are no controlled data on which to base recommendations for a specific therapeutic regimen for lung abscess. Antibiotic therapy is indicated in all cases, and drainage should be considered in selected patients, particularly in those with severe and extensive disease, progressive signs, and those who are severely malnourished or otherwise immunocompromised. This is the same group that requires more aggressive diagnostic approaches, because of the wide spectrum of possible etiologies. Despite the good outcome in the vast majority of patients, this is still a potentially lethal condition in some children.

Chlamydia Pneumonia

There are two major types of chlamydia pneumonia: (1) psittacosis (ornithosis) and (2) pneumonia due to *Chlamydia trachomatis.*

Psittacosis

Psittacosis is usually seen in individuals in contact with birds. Thus, poultry and aviary workers,[239] veterinarians,[249] zoo-keepers, pet store personnel, and pet owners have been afflicted. Although the disease is communicable by the aerosol route from highly symptomatic patients, outbreaks are more commonly associated with enzootic infections often traced to the sale of tropical birds. Psittacosis is usually acquired by inhalation of the infected secretions or droppings.

The patient with psittacosis usually has a rather abrupt onset of high fever, toxicity, bradycardia, and tachypnea. The white blood cell count may be depressed and cough is prominent. Chest radiograph reveals a patchy bronchopneumonia and occasionally areas of consolidation are noted. The disease can spread rapidly throughout the lungs, and if untreated, a mortality rate of 20% may be associated with this condition. Treatment with chloramphenicol or tetracycline should be instituted early and continued for approximately 2 weeks. The oral route is satisfactory, although some patients may require parenteral drug therapy during the initial stages when extreme toxicity or vomiting may make oral medication impractical.

Chlamydia trachomatis Pneumonia

Epidemiology Approximately 3–25% of pregnant women in North America have cervical chlamydia infections. As many as 10% of the infants born to these mothers may develop pneumonitis at 1–3 months of age. Thus, the occurrence of chlamydia pneumonia of infancy may be as frequent as 5–40/1000 live births. It is clear that *Chlamydia trachomatis* is responsible for more than the infantile pneumonia syndrome, since 25% of children develop serologic evidence of infection by 10 years of age.[36] Chlamydia may also be a cause of respiratory infection and pneumonia in adults, as suggested recently by serologic evidence of chlamydia infection in 4/19 adults with idiopathic pneumonia syndromes.[187]

Etiology. *Chlamydia trachomatis* serotypes D-K are most frequently implicated in chlamydia pneumonia. These are small organisms with a cell wall and contain both DNA and RNA. Although they divide by binary fission, they require an intracellular environment for reproduction. These characteristics are reflected by the formation of inclusion bodies in infected respiratory epithelial cells, which can be seen in smears of eye discharge or conjunctival scrapings, tracheobronchial respiratory epithelium, and in tissue culture, when stained with giemsa, periodic acid-Schiff (PAS), or fluorescent-tagged antibody.

Clinical Manifestations. Chlamydia pneumonitis is marked by a gradual onset of cough, poor weight gain, rapid breathing, and nasal congestion. Approximately half of these patients also have conjunctivitis, although chlamydia may be found in the eyes of almost all of these patients. Most remarkably, these patients do not have fever and their cough is paroxysmal in nature. It has been called "staccato" because of its repetitive nature, and is not associated with an inspiratory whoop, as is seen with pertussis.[142] Infants who have conjunctivitis in the first 2 weeks of life may develop a pneumonia syndrome 2–4 weeks later. Occasionally, secretory otitis media is also associated with chlamydia pneumonitis.

Rales are described in the majority of these patients, although the infection is predominantly interstitial and may not be associated with any auscultatory findings. Patients have been noted to wheeze in cases of chlamydial pneumonia as well.[279]

Diagnosis. The diagnosis is suggested by the presence of cervical Chlamydia infection in the mother, or by Chlamydia conjunctivitis in the newborn, or both. The cough and lack of fever are also quite characteristic. Chest X-ray reveals bilateral interstitial infiltrates with some hyperaeration. Blood gas analysis usually reveals a low $\mathrm{Po_2}$. Peripheral blood eosinophilia of 300/mm^3 or more and hyperglobulinemia (IgG and IgM) are also consistent characteristics.[332]

The diagnosis is confirmed by isolation of *Chlamydia trachomatis* in tissue culture or by serologic demonstration of an immunofluorescent antibody titer of 1/32 or more.

Pathologic examination of lung tissue from these infants reveals interstitial infiltration with lymphocytes, plasma cells, eosinophils, and moderate fibrosis.

Treatment. Erythromycin and sulfisoxazole are both active against *Chlamydia trachomatis* and can be used in infants. Erythromycin, being somewhat less toxic, is most frequently prescribed in a dose of approximately 50 mg/kg/day for 14–21 days (either the estolate or ethylsuccinate form has been used). Some infants are benefited by chest physiotherapy as well. Clinical improvement is usually seen within 7 days of institution of antibiotic therapy.[26] Where microbiologic criteria are available, these should be used to confirm sterilization of conjunctival and respiratory surfaces, events likely to decrease communicability.

The long-term outcome in this condition is excellent since recurrences or chronic sequelae have not been described. The true scope of chlamydial infections in pediatric patients remains to be defined.

Pertussis

Epidemiology

Pertussis is still a major cause of morbidity and mortality worldwide. In developing countries, pertussis is often life-threatening, especially in newborns and young infants, in malnourished hosts, and in infants with measles or tuberculosis.

Pertussis, commonly known as whooping cough, is highly communicable. Attack rates of 80–100% have been observed within family units and in isolated populations.[227] In developing countries, attack rates are highest in infants in the first year of life.[42] The disease is slightly more prevalent in girls and is seen throughout all seasons. No inanimate or animal reservoirs for *Bordetella pertussis* have been defined, although *Bordetella bronchiseptica* (parapertussis) is enzootic in cats, rodents, chickens, and other animals. Recent data indicate that some immunized humans may be asymptomatic carriers of *B. pertussis*.[43] This reservoir may be particularly important in hospital outbreaks.[244]

Pathogenesis

Bordetella pertussis is a complex organism elaborating a variety of substances with various physiologic effects. Some of these stimulate lymphocytosis and others are encephalopathic in experimental animal infection. The exact mechanism that stimulates prolonged and recurrent lower respiratory symptoms in humans has not been defined. Pertussis endotoxin is probably important in the adjuvant effect provided by this vaccine, as well as in the pathogenesis of the disease and some of the vaccine's side effects.

Etiology

The major cause of whooping cough is *Bordetella pertussis*. A similar syndrome can be caused by *Bordetella bronchiseptica* and is occasionally seen in association with respiratory infections of animals. Although adenoviruses, influenza, parainfluenza, and other agents have been isolated in patients with pertussis syndromes, these isolates are predominantly found in those already infected with *Bordetella pertussis*.[179] Whether these agents act in concert or in sequence is not clear. It is also possible that some agents, such as adenovirus, may be reactivated in pertussis.

Clinical Manifestations

The classic stages of pertussis and their durations are outlined in Table 5-11. The catarrhal phase is usually indistinguishable from other upper respiratory infections, since cough is sporadic and mild, the temperature is seldom above 38.5°C, and conjunctival involvement is a minor and inconsistent component. The diagnosis is usually considered in the index case during the paroxysmal stage. Coughing spells followed by an inspiratory whoop and vomiting of secretions are the major features of this stage. Sometimes, facial and eyelid swelling, hemorrhagic and pressure phenomena (outlined under complications), and encephalopathy are also noted.

Although the cough initially is most marked at night, during the height of the illness it becomes easily stimulated during all hours of the day. Newborns are prone to apnea and to atelectasis and diffuse bronchopneumonia early in their course.[58] Leukemoid reactions are also seen in newborns, but the characteristic paroxysmal cough may be absent.[219] Fatal

TABLE 5–11. Clinical Stages of Pertussis (Whooping Cough)

	Duration	*Manifestations*
Incubation period:	5–10 days	None
Catarrhal phase:	1–2 weeks	Coryza Cough Mild fever Tearing
Paroxysmal phase:	3–8 weeks	Paroxysms of cough (especially nocturnal) Vomiting Whoop (inspiratory stridor) Thick, copious secretions
Convalescent phase:	3–12 months	Cough Recurrent and paroxysmal Cough with URI

pertussis is more frequent in newborns, emphasizing the need for careful treatment of the infection in late pregnancy.[214]

Diagnosis

The diagnosis of pertussis is generally made on the basis of epidemiologic information and clinical tests. Since communicability is so high and subclinical infection rare, a history of exposure to an individual with pertussis is often present. Similarly, a history of absent or incomplete immunization supports the diagnosis. The clinical features of the paroxysmal stage are distinctive enough to characterize the infection in many cases.

The etiologic diagnosis of pertussis can be made most conveniently with the use of respiratory secretions obtained from the nasopharyngeal area. This can be done by swabbing or suctioning techniques;[359] generally the results are better if the nasopharyngeal swab stimulates a coughing episode. The most rapid means of identifying the bacteria in these secretions is by the fluorescent antibody technique. Unfortunately, the quality of the reagents and the expertise required make the test inadequate in many instances. False-positive results of up to 30–40% have been reported in some series, and false-negative results of over 50% in others. Therefore, the most exact diagnosis is made by bacteriologic culture. This is also not easy, since media must be prepared from fresh blood (Bordet-Gengou agar). The addition of charcoal and/or penicillin has been useful in selecting these organisms as well. When plates are prepared fresh, and the nasopharyngeal secretions are inoculated quickly, the bacteriologic results can be very accurate.

An indirect test that suggests pertussis include lymphocytosis. Leukemoid reactions consisting of predominantly mononuclear cells (i.e., above 30,000 white blood cells[3]) are highly suggestive of the diagnosis in the context of appropriate clinical symptoms. The physical examination and chest X-ray are rarely specific. A "shaggy heart" radiographic picture represents the diffuse bronchopneumonia that is characteristically seen in pertussis in young infants. Some patients have inappropriate secretion of antidiuretic hormone with attendant edema and hyponatremia, but this is not specific for pertussis. Testing for pertussis agglutinins or ELISA antibodies may provide evidence of prior immunization or infection, but these procedures are not widely available and are poorly standardized.[228]

Therapy

The most important elements of management of pertussis are supportive care for the patient and prevention of spread of infection to susceptible contacts. Supportive care is most needed in young infants where repeated vomiting, episodes of hypoxemia, mucus aspiration, and seizures may be life-threatening.[206] Occasionally, these patients have pneumothorax, atelectasis, and/or pulmonary bacterial superinfections, which may require aggressive management as well. Hospitalization and careful observation of young infants are often required. Refeeding after vomiting, parenteral nutrition, hydration, suctioning, a quiet environment, clean air, and frequent monitoring of vital signs are all important components. Increasing sleeping respiratory rates will provide clues to hypoxemia, pneumothorax, and atelectasis. These can be confirmed by appropriate radiographic and blood gas measurements and require specific remedial action.

Erythromycin is the most active antibiotic in vitro against *Bordetella pertussis.* It rarely shortens the clinical course, but may decrease communicability. It has been suggested that it can shorten the course of illness if therapy is instituted early in the catarrhal phase as well. Generally erythromycin estolate 50 mg/kg/day is administered in four divided doses. Therapy is usually continued for 14 days in an effort to completely eradicate the organism. Where accurate bacteriologic monitoring is available, this course may be shortened if supported by negative culture results. Some experience suggests that *Bordetella pertussis* is eliminated from the nasopharynx by 7 days in the majority of patients;[17] however, others report that almost half of the patients may still harbor viable bacteria 4–7 days after the initiation of erythromycin or trimethoprim/sulfamethoxazole.[152]

Hyperimmune pertussis globulin has been shown to be of no value in the therapy of pertussis.[16] A controlled study of hydrocortisone sodium succinate, 30 mg/kg/day for 2 days, then tapered over 5–6 additional days, demonstrated a reduction in cough, whoop, and vomiting, particularly in infants under 1 year of age.[368] The diagnosis was made clinically, the outbreak was relatively mild (no deaths in 72 hospitalized infants under 1 year and no complications other than pneumonia reported), and no confirmatory controlled reports have appeared since 1973. Despite these reservations, this therapy deserves consideration in young, seriously ill infants receiving appropriate antibiotics, nursing care, and observation.

Complications

A recent survey of complications of pertussis in the United States revealed seizures in 4% of 1277 patients and death in 0.5%; all cases of encephalopathy and death occurred in the first year of life.[58] Complications associated with pertussis are generally referable to the high pressures generated during paroxysms of cough, the increased quantity and thickness of secretions, and the systemic effects of the infection, the pathogenesis of which is often unexplained. Hence, the patient may have epistaxis, petechial hemorrhages, umbilical and inguinal hernias, rectal prolapse, and even subcutaneous or mediastinal emphysema.

Bronchitis and bronchopneumonia are common features of pertussis, being most prevalent in young infants. Atelectasis and pneumothorax may also be seen. Otitis media is occasionally associated with pertussis, although it is not clear whether this is due to associated viral infection or dysfunction of eustachian tube clearance by the thick and copious secretions.

A fascinating feature of the convalescent stage of pertussis is the recurrence of cough, sometimes including paroxysms and vomiting, for several months after the acute illness. These may develop during a common cold or other upper respiratory viral infection. In practice, this is commonly forgotten, and parents become frightened and discouraged that their nightmarish experience with classic pertussis is starting all over again. Clinicians should remember to advise parents about this probability during the convalescent stage. If frequent respiratory infections can be avoided during recovery, they should be. This is most important in the young infant.

The encephalopathy noted with pertussis is rare, but can have serious consequences. It is most frequently seen in young infants and may be due to episodes of hypoxia, aspiration of thick mucus, and/or coughing spasms. Episodes of atelectasis and pneumothorax may also be associated with extreme changes in intrathoracic pressure, hypoxemia, and cerebral petechiae. The encephalopathic changes may be manifest by convulsions, coma, drowsiness, lethargy, and/or irritability. Some sequelae are occasionally seen years after these events.

The long-term complications of uncomplicated pertussis, bronchitis, and bronchopneumonia are rare. Although the older literature suggests that bronchiectasis and/or pulmonary emphysema may follow, this most likely represented superinfection by tuberculosis or Staphylococcus. At present, there should be few pulmonary residua of pertussis, although neurologic sequelae may persist.

Prevention

In recent years more has been written about this aspect of pertussis than about any other.[231] This is a consequence of the frequency of side effects noted with the vaccine and the false sense of security created by the low incidence of disease and its milder course in well-immunized populations. Public concern for adverse effects resulted in a marked drop in vaccination in Great Britain recently.[238] Subsequent outbreaks of clinical pertussis[116] involving 65,785 patients and 14 deaths in 1982 in England are evidence of the inadequacy of this approach. There is no doubt that the currently available vaccine is not completely satisfactory; however, it is effective in preventing much serious disease.[97] There is also little doubt that the natural disease has the potential for much more severe consequences than those of immunization.[133] Efforts to develop a better vaccine are to be applauded.[116] In the meantime, adequate immunization of all susceptible individuals should begin as early in infancy as is possible. It is generally begun at 2 months of age; however, in areas of high pertussis endemicity, immunization should be commenced in the newborn period.

Approximately half of pertussis vaccine recipients will experience local pain, swelling, and redness around the injection site (Chapter 1). Fever is also seen in the same percentage of patients, as is fretfulness and irritability. About a third of infants become drowsy and about 20% lose their appetite within 48 h of vaccination. Parents should be warned about these side effects and appropriate aspirin or acetaminophen therapy prescribed. If they are not warned, parents become inappropriately concerned, as does the physician, about the toxicity of the vaccine. The duration of these effects is generally limited to 24 h in most cases and they are usually seen within the first 48 h of immunization. They are more frequent after the first and second doses of vaccine. Marked local and/or systemic reactions with pertussis vaccine should preclude subsequent immunization.

Rarely, convulsions and serious neurologic consequences of vaccination are encountered; however, infantile spasms may be triggered (but are not caused) by pertussis.[27] Most recent estimates of the frequency of this complication suggest that brain damage occurs in 1/100,000 children immunized with pertussis vaccine. Contrast this with the 27 deaths seen in 100,000 cases of pertussis in Great Britain recently. In general, patients with a history of convulsions, or those recovering from central nervous system infection (i.e., meningitis, meningoencephalitis, etc.), should not receive pertussis vaccine. Patients with a strong family history of epilepsy probably also should not be vaccinated.

The risk of toxicities from the vaccine begin to approach the risk of adverse effects from the disease in individuals of school age and in adults. This consideration, and the current rarity of endemic pertussis in the community in members of these age groups, suggest that pertussis vaccine should not be given to individuals over the age of 6 years.

In certain situations, consideration of vaccination of adults should be viewed differently. One outbreak in an adult population during a hospital epidemic was so severe that 0.2 ml of pertussis vaccine was used to boost immunity in previously immunized adults.[207] This, and the use of erythromycin, was associated with ending the epidemic, although the role of each individual approach is unclear. Somewhat discouraging, however, was the report that two adults developed generalized rashes with this small dose of vaccine, one requiring systemic corticosterioid therapy.

Different serotypes are prevalent in certain countries and different vaccine products are required.[47] Hence, both vaccine efficacy and toxicities must be viewed cautiously before global generalizations are made about efficacy or toxicity.

Other preventive measures appropriate for consideration in preventing the spread of pertussis to susceptible contacts include the use of antibiotics and isolation procedures. The disease is spread predominantly by respiratory aerosolization, as well as direct contact. Hence, wearing masks and gowns, as well as handwashing, are indicated. The gowns are necessary because infants with this condition have copious secretions and frequent vomiting or regurgitation. When hospitalized, these patients should be housed in rooms with negative pressure exteriorized ventilation. The only individuals allowed in the room should be those also infected with pertussis, or appropriately masked and gowned relatives and caretakers. Erythromycin can be administered to family contacts and, occasionally, to individuals in other closed populations (i.e., newborn nurseries) exposed to individuals with symptomatic pertussis.[4] Although this prophylactic maneuver is reported to be effective, in some instances disease has developed despite the use of erythromycin. Nonetheless, considering the availability and low toxicity of the drug, erythromycin prophylaxis of close contacts and early treatment of the index case seem useful adjunctive maneuvers in prevention of spread of the infection. Immunity acquired after natural pertussis is probably superior to that seen with immunization and, therefore, should not be followed by vaccination of the index case. The disease in the index case should, however, remind us to boost and adequately immunize other contacts. Hyperimmune pertussis globulin has no effect on the prevention of this disease.

Mycoplasma

Epidemiology

Mycoplasma pneumoniae is one of the commonest causes of respiratory infections in man. The vast majority of cases are expressed as upper respiratory infection, pharyngitis, tracheitis, or bronchitis, and are self-limited. Less than 10% of patients have clinically apparent pneumonia, yet these amount to approximately 20% of cases of pneumonia in patients over the age of 5 years.[51] The infection is prevalent throughout temperate climates and should be thought of in situations where several members of a family, or other closed populations, have prolonged cough and fever. The disease is becoming more frequently recognized as improvements in diagnostic procedures are made.

Etiology

Mycoplasma pneumoniae is the primary agent causing most of the cases of pneumonia described above. Nevertheless, the organism is often present in conjunction with other respiratory viruses, particularly adenovirus. It can also be seen in association with Epstein-Barr virus infectious mononucleosis.[81]

Clinical Manifestations

The most typical picture is characterized by a brief prodrome of upper respiratory signs followed by persistent cough and fever. Myalgia, malaise, arthralgia, and weight loss may also be seen. As many as 20% of patients with pneumonia will also develop pleural effusion. This may be seen only in lateral decubitus X-rays.[107] In a small percentage of patients pneumatoceles and lobar consolidation are present as well.[51] The usual presentation is chronic cough with a surprisingly abnormal chest radiograph, considering the lack of clinical and auscultatory findings. This is usually a mixed alveolar-interstitial pattern, most marked peribronchially. The organism is located mainly within the lumen of the tracheobronchial tree and the predominant pathology is bronchitis and bronchopneumonia. Thus, rhonchi may be present, but rales are infrequent. Pleuritic pain and extrapulmonary manifestations may also be present (see Complications below). Many times, *Mycoplasma pneumoniae* is the precipitating cause for attacks of asthma or acute respiratory exacerbations in patients with cystic fibrosis or other chronic pulmonary diseases. Respiratory failure and fatalities can occur.[114]

Diagnosis

When suggested by the clinical and epidemiologic features, a chest X-ray will often reveal diffuse pulmonary infiltrates (Fig. 5-4). Some of the extrapulmonary manifestations of mycoplasma infection may also suggest the diagnosis. Most characteristic are hemolytic anemia and neurologic syndromes.

Approximately 70% of patients with *Mycoplasma pneumoniae* infections elaborate an IgM antibody capable of agglutinating red blood cells at 4°C (cold agglutinins) (Fig. 5-5). This is a transient phenomenon, however, and is not specific for this infection, since it can be seen in a variety of respiratory viral infections, infectious mononucleosis, and several autoimmune conditions. If present in titers greater than 1:64, it is suggestive of mycoplasma infection, in the appropriate clinical setting. If the mycoplasma complement-fixation titer is also above 1:64, these serologic tests together are highly supportive of the diagnosis of *Mycoplasma pneumoniae* infection. Fourfold titer rises of mycoplasma complement-fixing antibody are more specific, although some cross-reactivity with human tissue antigens (particularly brain and red blood cells) need to be considered in interpreting serologic evidence of infection.[183] Culturing *Mycoplasma pneumoniae* from upper or lower respiratory secretions is diagnostic, but technically difficult and not widely available. The most limiting factor, perhaps, is the slow growth of these organisms in vitro.

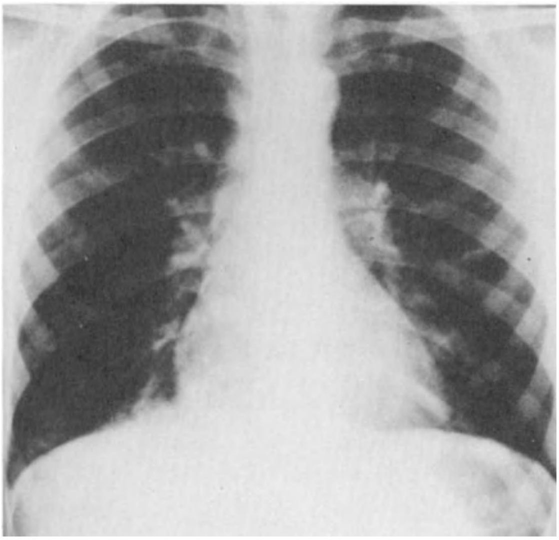

Figure 5–4.

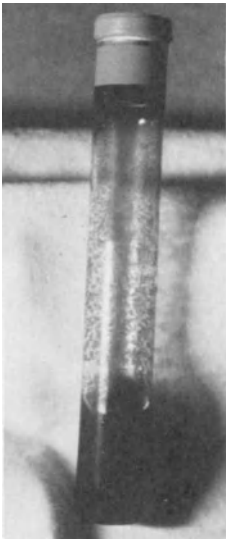

Figure 5–5.

Figure 5–4. Mycoplasma pneumonia.

Figure 5–5. Cold agglutinins demonstrated by a rapid bedside method.

Treatment

When diagnosed, or strongly suspected, mycoplasma pneumonia should be treated with erythromycin or tetracycline. Both drugs shorten the duration of fever and malaise; however, sterilization of the respiratory secretion is rarely achieved.[51] A 2-week course is recommended, although most patients become afebrile, and show marked clinical improvement within 3–4 days.

Complications

Diverse manifestations of *Mycoplasma pneumoniae* infections may occur, with or without the presence of pneumonia (Table 5-12). Some of these can be life-threatening, such as the neurologic complications. The most severe of these are Guillain-Barré,[22] a poliomyelitis-like syndrome,[344] and cerebral infarction.[251] These complications are suggested when they occur together with pneumonia and the appropriate serologic antibody response. It must be remembered that some cross-reactivity is seen between human brain tissue antigen and mycoplasma complement-fixing antibodies.[183] In one recent case of Guillain-Barré neuropathy, however, evidence is presented that suggests a direct causal effect of the organism.[22]

The hemolytic anemia that is noted with *Mycoplasma pneumoniae* infections can be of sudden onset and massive.[261] This is probably related to autoantibodies produced against the red blood cell I antigen which is similar to a mycoplasma antigen.

TABLE 5–12. Complications of Mycoplasma Pneumoniae Infections

- Pleural effusion
- Hemolytic anemia (often Coombs-postive)
- Acute renal failure
- Nephritis
- Myocarditis
- Hepatitis
- Neurologic dysfunction
- Meningoencephalitis
  - Guillain-Barré
  - Cerebral infarction
  - Polio-like syndrome
- Mucocutaneous reactions
  - Macular
  - Erythema-multiforme (Stevens-Johnson)
  - Toxic-epidermal necrolysis
  - Vesicular
- Arthritis

Some of the skin and cutaneous manifestations associated with *Mycoplasma pneumoniae* infections are also bizarre and include vesiculobullous eruptions,[321] vesicular eruptions,[68] and severe erythema multiforme or Stevens-Johnson syndrome. In the latter, ocular involvement may lead to severe corneal scarring.

Renal failure has also been described in association with mycoplasma infection.[285] The pathogenesis of this complication may be due partly to massive hemolytic anemia, but also to acute tubular and interstitial nephritis.[253]

Prognosis

The vast majority of patients with *Mycoplasma pneumoniae* infections do not come to medical attention. Those with pneumonia recover completely in most instances. In a small proportion of patients, respiratory infections are recurrent or prolonged. Among the extrapulmonary manifestations of *Mycoplasma pneumoniae* infection, those with neurologic involvement portend the gravest prognosis. Respiratory isolation should be instituted to prevent spread of this infection in hospital.

Pulmonary Tuberculosis

Epidemiology

Globally, tuberculosis is still a major cause of morbidity and mortality. The predominant organ of involvement in tuberculosis is the lung. However, multisystem involvement is common. The reader is also referred to the discussion of tuberculosis in newborns (Chapter 3), and to the section on bone and joint infections (Chapter 8). The lung has a demonstrable focus in approximately a third of cases, in which the most dramatic clinical manifestations are extrapulmonary. The respiratory tract is the proposed entry point for *Mycobacterium tuberculosis* in almost all cases.

The clinical expression of tuberculosis infection is extremely variable and depends on the state of nutrition, age, and underlying and concurrent conditions of the host.[162] The incidence of infection depends on hygiene, control measures, and reporting. There is little doubt that this disease preys on the already distressed lower socioeconomic classes in crowded, urban populations.[163] Those malnourished and otherwise debilitated are at the highest risk. Some of these epidemiologic characteristics are illustrated in North America. Here, Indian and Eskimo populations, and some large urban inner-city groups, still have high rates of tuberculosis in infancy and childhood. In 1977, in the USA, there were approximately 30,000 cases of tuberculosis reported and 3000 deaths. This represents a case rate of 14/100,000 population and a fatality of 1.4/100,000.[123]

Part of the difficulty of controlling tuberculosis lies in the asymptomatic or nonspecific clinical expression of disease, late diagnosis, and prolonged therapies required for adequate control. Reactivation of infection is also contributory. The communicability of pulmonary tuberculosis is variable. In the open community, it appears to be low, although it is higher in certain populations, as mentioned above. For example, discovery of clinically symptomatic disease in a high school student in the United States led to the detection of skin test positivity in 77% of 379 students in the same school.[78]

Pathogenesis

Mycobacterium tuberculosis has several characteristics that differentiate it from common bacteria. It is relatively resistant to many drugs, multiplies slowly, and is capable of remaining viable within macrophages and tissues for long periods.[210] Tuberculosis, in this respect, resembles other facultative intracellular parasites such as Brucella, Listeria, Salmonella, and *Francisella tularensis.* Infection associated with this organism is also characterized by immunosuppression related to the extent of infection. Thus, the very ill patient may have a negative skin test despite widespread presence of the organism throughout the lung and other tissues. Pulmonary tuberculosis, in certain respects, is better understood by examining the epidemiology and pathogenesis of leprosy than by comparisons with acute bacterial infections. A useful outline of the pathogenesis and expression of tuberculosis is presented in Fig. 5-6.

Some of the factors predisposing the patient to tuberculous infection have been mentioned above. In addition, trauma,[86] intercurrent infections with measles or infectious mononucleosis, bleeding disorders,[25] and immunosuppression may predispose the host to more serious primary in-

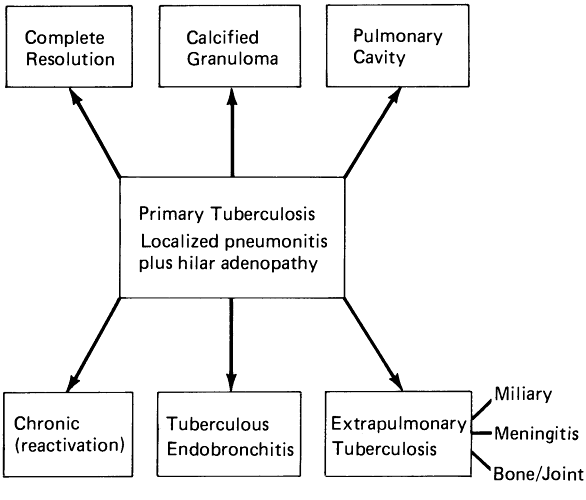
Complete Resolution
Calcified Granuloma
Pulmonary Cavity
Primary Tuberculosis
Localized pneumonitis plus hilar adenopathy
Chronic (reactivation)
Tuberculous Endobronchitis
Extrapulmonary Tuberculosis
Miliary
Meningitis
Bone/Joint

Figure 5–6. The pathogenesis and expression of tuberculosis.

fection or reactivation of an existing pulmonary focus. Many of these factors are interrelated, and, in fact, there is doubt that measles alone will have a deleterious effect on tuberculosis in the normal host.[112] For example, preliminary evidence suggests that genetic factors are involved in the high rates of disease in Eskimo and Indian populations. Genetic susceptibility may also be reflected by the predominance of the HLA Bw15 haplotype in black patients with tuberculosis.

Clinical/Radiographic Manifestations

The majority of patients who inhale *Mycobacterium tuberculosis* manifest signs that are indistinguishable from those of upper respiratory infection or self-limited bronchitis or bronchopneumonia. Some patients develop a more marked cough and fever syndrome associated with primary infection, but even these tend to be self-limited with the formation of a single or multiple granuloma associated with some hilar lymphadenopathy.[162] Some granuloma can be seen on chest radiograph during this stage, but others only manifest as a calcified lesion several months or years later.

A small percentage of patients are not able to contain the primary pulmonary infection and develop more widespread bronchopneumonia, or, less commonly, endobronchial tuberculosis or miliary disease. The latter two are usually characterized by high fever and marked toxicity. In young infants, meningitis and other life-threatening extrapulmonary manifestations are not uncommon. Occasionally, pneumothorax can be a presenting sign or a complicating feature early in the course of pulmonary tuberculosis.[161]

Those who ingest the organisms (this is predominantly restricted to populations drinking raw milk) may develop cervical adenopathy and/or gastrointestinal tuberculosis.

Reactivation tuberculosis is most commonly seen as a segmental or pneumonic infiltrate. The radiographic and clinical picture can seldom be relied upon to differentiate reactivation from primary disease. Nor can radiographs distinguish the etiology with any degree of certainty. A miliary pattern on chest X-ray is, however, highly suggestive. Nevertheless, bacterial, viral, and fungal pneumonias should be considered in the differential diagnosis.

Fever is seen in approximately 80% of cases of pulmonary tuberculosis.[181] As mentioned above, younger children and infants are more likely to have meningitis and other associated extrapulmonary manifestations. These can include skin, oral, ocular, central nervous system, skeletal, or cardiovascular diseases.[250] The incidence of these extrapulmonary manifestations can be as high as 30%, warranting aggressive diagnostic procedures in cases of pulmonary tuberculosis.

The classic symptoms of tuberculosis, such as fever, night sweats, weight loss, chronic cough, and hemoptysis are seen more commonly in the school-age child and young adult than they are in early infancy. Manifestations in young children may be extremely nonspecific, although the presence of persistent cough and weight loss should alert the physician to the possibility of tuberculosis. Erythema nodosum, phlyctenular conjunctivitis, and clubbing are occasionally noted.

Diagnosis

The diagnosis of tuberculosis depends largely on suspicion provided by epidemiologic history. Although pulmonary disease is the most frequent initial manifestation, the first sign to suggest the diagnosis may be neurologic or hematologic. Some of these patients have anemia and a few have neutropenia and pancytopenia, often associated with pulmonary and/or miliary tuberculosis.[94] Cough and fever in North American Indian and Eskimo populations, and in others from countries where tuberculosis is endemic, should be considered as tuberculosis until proved otherwise.

The skin test remains the clinician's best tool for the diagnosis of asymptomatic or symptomatic tuberculous infection.[190] Some prefer to use the term "tuberculous infection" for all individuals with positive skin tests, while reserving the term "tuberculosis" for individuals with positive skin tests manifesting clinical signs and symptoms. Others add microbiologic criteria, feeling the clinical and skin test features are too nonspecific. Positive skin test reactivity is defined as induration of 10 mm or more after skin testing with intermediate strength (5 tuberculin units) purified protein derivative (PPD). These reactions remain positive for years after isoniazid therapy.[157] Care must be taken in preparation of skin test material, and in the administration and interpretation of the test. The qualities of the antigen and test method are variable and have led to controversies about the use of the Tine® test,[155] patch testing (Heaf test), and the use of varying strengths of PPD. Add to this the effect of prior sensitization by BCG, atypical mycobacteria or other related antigens, and the confusion is understandable. Further, some patients are even allergic to the phenol contained in the PPD diluent!

Despite the above shortcomings, the vast majority of patients with pulmonary tuberculosis have a positive skin test reaction to 5 tuberculin units of stabilized PPD. Those with induration of 5–10 mm may have atypical mycobacterial infection, past BCG immunization, or early illness. Delayed hypersensitivity is usually detectable 2–4 weeks after infection. Remember, however, in newborns and young infants, skin test hypersensitivity may not develop for 2 or 3 months after initial infection. Intercurrent disease, overwhelming tuberculosis, malnutrition, sarcoidosis, and other anergic states may be sources of false-negative skin tests as well.[146] There is also a small percentage of patients with non-life-threatening pulmonary tuberculosis who do not appear to develop hypersensitivity at any stage during their disease.[309] The only way to confirm the diagnosis in these children is by microbiologic culture.

False-positive hypersensitivity may be due to experience with cross-reacting organisms, as mentioned above, and, rarely, to transfusion-acquired hypersensitivity. Pregnancy, or the concomitant administration of the tuberculin skin test with live vaccines, does not appear to alter the results of skin testing.[52] However, skin testing during a period of approximately 3–21 days after the administration of a live vaccine may lead to a false-negative skin test result.

In the final analysis, the following skin test procedures are recommended: Tine testing or other screening tests can be used in screening well children.[273] Any suspected positive reaction should be followed by careful intradermal skin testing with 5 tuberculin units of PPD (Mantoux). When patients are tested because of exposure to tuberculosis or are suspected of having tuberculosis, the Mantoux test should be used. Patients with a history of tuberculin hypersensitivity, and those with bacteriologically confirmed disease, should be tested first with lower concentrations of PPD. This will avoid large and potentially necrotic skin ulcerations after skin testing. Should these develop, topical applications of a corticosteroid may reduce the inflammatory reaction.

Microbiologic methods for diagnosis of tuberculosis include acid-fast smears of sputum and cultures. These are usually reliable, but false-positive smears can be seen due to the acid-fast appearance of atypical mycobacteria, Nocardia, Rhodococcus, and the Pittsburgh pneumonia agent. Moreover, the frequency of false-positive results is increased in smears of gastric aspirates due to ingested atypical mycobacteria and other acid-fast substances. False-negative results are commonly due to the presence of less than 10^5 *Mycobacterium tuberculosis*/ml of specimen. Culture of respiratory or gastric secretions on Lowenstein-Jensen media will confirm the diagnosis in most cases. Culture results may not be available for 6 weeks and may be rendered negative by previous therapy or inadequate specimen collection. Sampling of respiratory secretions by transtracheal aspiration[331] or fiberoptic bronchoscopy[99] is useful, if expectorated sputum cannot be acquired. The former must be limited to cooperative patients, usually those in adolescence or young adulthood.

In patients showing the presence of pleural effusion with pulmonary tuberculosis (parenchymal lesions are obvious in a little more than one-third of patients with tuberculous pleural effusions) pleural fluid and a pleural biopsy should be cultured. The latter should also be examined histopathologically. These procedures will yield the diagnosis in the vast majority of cases. In the child with miliary disease respiratory secretions and a liver biopsy should be cultured and examined histopathologically as well. The diagnostic yield of liver biopsy is very high in such patients.[119] Bone marrow examination and cultures, as well as biopsies of lung tissue, are also useful in selected cases. The importance of confirming a diagnosis microbiologically is twofold. First, the diagnosis should be secure, as management is long and expensive. Second, the in vitro susceptibility of the infecting organisms is important lest inappropriate medication be prescribed.

Other indirect tests, such as measurements of humoral antibody[28] or lymphocyte transformation,[75] are still under investigation. Every effort should be made to obtain a microbiologic diagnosis in all suspected cases of pulmonary tuberculosis. However, the management of these children should not be inappropriately delayed for these purposes, since the rate of progression of primary pulmonary tuberculosis in infancy and childhood is unpredictable.

Therapy

A positive skin test, in the absence of radiographic proof of pulmonary disease, usually mean the lesion is too small to be detected clinically or radiographically. Exclusion of extrapulmonary tuberculosis and an attempt to culture *Mycobacterium tuberculosis* from the respiratory or gastrointestinal secretions and urine should be made. Subsequently, when these are negative, the asymptomatic child with a positive skin test should receive isoniazid (INH) 10 mg/kg/day (maximum 300 mg/day), given once daily, for approximately 1 year. Beyond puberty, pyridoxine 15–50 mg/day should also be administered to avoid the development of peripheral neuritis. Patients with positive skin test result exposed to INH-resistant tuberculosis may require a year's therapy with both INH and rifampin. Such therapy should be restricted to 10 mg/kg of INH and 15 mg/kg of rifampin (maximum 600 mg/day) and should be monitored clinically and with quarterly liver function tests. This is because the combination of drugs seems to enhance the likelihood of hepatotoxicity.[35] This complication of combined therapy may occur in as many as 3% of children and is usually noted within the first 90 days.[55]

The treatment of symptomatic pulmonary tuberculosis should include at least two drugs. If the infecting bacteria are known to be sensitive, INH combined with rifampin is the preferred regimen. Doses of 10–20 mg/kg/day of each drug to the maximums listed above should be used. Remember to add pyridoxine for patients beyond puberty. Both drugs should be continued for a period of 9 months.[306] With such a program of therapy, the fever will resolve in two-thirds of patients within 2 weeks.[181] Some patients with more advanced disease, including those with cavitation, may require 8–12 weeks before fever disappears. Although most of these predictions are gathered in experience with adult patients, children tend to respond even more quickly than adults. The rate of bacterial sterilization of the lesions may be slower, although several studies have indicated that viable organisms are often not recoverable within a few days to two weeks after institution of appropriate antituberculous therapy. In the vast majority of patients the sputum is sterilized within 6 weeks of the beginning of treatment.

Resistance to antituberculosis therapy is becoming more of a problem. In the United States, approximately 5% of urban cases are resistant to INH and streptomycin. This can be as high as 12% in the Hispanic populations of California and New York City.[56] In other areas of the world, such as Indo-China, as many as 33% of individuals will be infected with INH-resistant bacteria.[57] When this situation is suspected, for epidemiologic reasons or by virtue of exposure to a patient with known resistant organisms, therapy for pulmonary tuberculosis should be initiated with four drugs. Usually, INH, rifampin, ethambutol 15 mg/kg/day, and pyrazinamide 15–30 mg/kg/day (2 g maximum) are prescribed. Restriction of pyrazinamide therapy to 2 months is effective and reduces the drug's toxicity.[8] If suspension is not available, the contents of rifampin capsules can be mixed with applesauce or jelly.[96] When bacterial cultures and sensitivities are available, an appropriate two-drug regimen can be selected. Other second-line drugs that may be required for treatment of primary or reactivation pulmonary tuberculosis include viomycin, capreomycin, kanamycin, ethionamide, para-aminosalicylic acid (PAS), and cycloserine.[362] See Chapter 2 for specific doses and properties of these drugs.

Other aspects of the management of pulmonary tuberculosis include consideration of isolation of the patient (see Prevention below), maintenance of optimal nutrition, eradication of predisposing factors and intercurrent illnesses, and careful followup. The followup should include microbiologic examinations to document sterilization of the sputum, appropriate management of extrapulmonary foci, and repeat radiographs at 3–4 month intervals to document resolution of pulmonary lesions. More frequent radiographs, scans, or other examinations of pulmonary lesions are rarely useful.

Miliary tuberculosis, or pulmonary tuberculosis associated with wide endobronchial spread and severe toxicity, may require adrenal glucocorticosteroid therapy for a brief period, generally not longer than 1 month. This is in an effort to improve the sense of well-being of the patient, restore appetite, and decrease subsequent pulmonary fibrosis. Clinical experience suggests that these effects are obtained with the use of steroids, although controlled studies are lacking.

There are few complications of adequately treated pulmonary tuberculosis, since restoration of nutrition and appropriate antimicrobial therapy are associated with recovery in most children. The patient can be managed at home; however, compliance with the treatment needs to be stressed.

Prevention

The ideal solution to the global problem of tuberculosis would be the development of an effective vaccine. Unfortunately, the only vaccine available, BCG, is not consistently effective (Chapter 1). Part of the problem lies in the use of various strains and concentrations of bacteria used to prepare the vaccine, as well as different infecting strains of tuberculosis in certain communities. Prospective controlled trials have shown efficacy rates of 0–80%; a recent trial in India showed little protective effect of BCG, but this assessment did not include infants and children, some of the populations at highest risk for dissemination.[93] Despite the controversy, the vaccine is relatively safe and can be a useful adjunct in the prevention of tuberculosis in infants persistently exposed to untreated cases and in populations where skin test conversion rates exceed 1% per year.[54] Whenever practical, use of BCG should be followed by Mantoux skin testing 2–3 months later, in order to establish a baseline for skin testing reactivity. Again, the effects of BCG on subsequent skin test reactions are variable, although some guidelines are available. These generally suggest that young infants receiving BCG rarely have skin test reactivity greater than 10 mm of induration later on in childhood and into adult life.[172]

Chemotherapeutic prophylaxis is also useful. The problem here lies in a balance of the risks and benefits. INH in adults over the age of 35 years is associated with hepatotoxicity, the incidence of which begins to approach the risks of tuberculosis.[329] This is less of a problem for children. Hence, INH is usually recommended for a year in patients under 35 years with skin test reactivity. Ten mg/kg/day should be used up to a maximum of 300 mg/day. In a US study of INH versus placebo in 2750 children, there was a 10-fold greater incidence of disease in those who received placebo as compared with those who received active drug.[100] Moreover, eight cases of meningitis were seen in the placebo group versus none in the drug group. Preliminary studies indicate that 6 months may be adequate to achieve the same effect in patients with normal chest radiographs.[100] In those patients exposed to INH-resistant tuberculosis, skin test conversion should prompt therapy with INH and rifampin for 9 months.[188]

The third line of prevention revolves around containment of spread. Although patients were formerly isolated in sanitoria, this is no longer practiced where effective chemotherapy is available. Most patients will not be infectious within 2 weeks of initiation of appropriate antituberculous therapy. Children with asymptomatic skin conversion or asymptomatic pulmonary disease are not considered to be infectious. Those who are coughing, those with acid-fast positive sputums, and those with cavitary disease should be considered infectious and their sputums shown to be free of acid-fast bacteria and viable mycobacteria before they are allowed to move freely in the community.[52] Some modified isolation procedures in the home can usually be instituted during this short period of time. The disease is predominantly spread by small aerosol droplets containing viable *M. tuberculosis.* There is no need to sterilize bedding, dishes, and clothing.

Pulmonary infection is the commonest manifestation of tuberculosis worldwide, but it is readily treated in infancy and childhood. The major problems include the reduction in active, untreated disease in adult populations and in the early diagnosis and careful management of pediatric cases. Public health resources need to be focused on specific populations shown to have high rates of tuberculosis and to be at high risk of developing tuberculous disease. It is often the alcoholic, debilitated grandfather who is the source of infection for the young child in the household.

Siblings and other family members, day-care and school contacts, and caretakers should be screened for active tuberculosis, or skin test reactivity, and appropriately managed, as outlined above. All asymptomatic close contacts with negative skin tests should be retested after 3 months. Young intimate contacts (under 4 years of age) are particularly prone to develop severe disease, including meningitis, as the initial expression of tuberculosis.[71] Hence, these contacts with negative skin tests should receive INH for 3 months; this can be discontinued if the skin test remains negative and the patient remains well.

Mycobacteriosis

Infection due to atypical mycobacteria is most commonly manifest in children as cervical or axillary lymphadenitis (see Chapter 4); however, the spectrum of disease is wide.[342] Pulmonary involvement is occasionally reported and includes endobronchitis,[265] pneumonia,[153] and mediastinal mass, which was recently reported in a 6-month-old.[180] Cutaneous and disseminated disease are also described.[131] Rarely, focal infections are associated with pulmonary or lymphatic disease, or are seen as part of disseminated infection in immunocompromised hosts.[357]

Mycobacteriosis is difficult to treat because of the variable susceptibility of the infecting organisms, their capacity to persist in intracellular sites, and the complexity of the host/parasite relationship, particularly in immunologically abnormal patients. Surgical approaches have been successful for isolated lymph node and cutaneous infection, and may occasionally be required in pulmonary disease as well. On the other hand, some of these bacteria may be particularly susceptible to common antimicrobials, such as erythromycin-sensitive *Mycobacterium chelonei,* allowing for successful medical treatment.[164] Even in these cases, however, treatment must be continued for 1–2 years and careful evaluation of the host's immune system is indicated.

Cystic Fibrosis

Cystic fibrosis is the most important cause of chronic obstructive pulmonary disease in children in North America at this time. This autosomal dominant disorder is seen in approximately 1:2000 North American Caucasians, although it is less commonly observed among blacks (1:17,000),[191] and is least common among the Mongoloid race (1:100,000). Dutch settlers in southwest Africa have the highest prevalence of this disease in the world (approximately 1:600).[319] The disease affects the exocrine secretions throughout the body. The diagnosis is usually made by detection of an elevated concentration of sodium and chloride in sweat, although the major clinical manifestations are referable to dysfunction of the pancreas and the respiratory bronchial mucus glands. Many of the nutritional abnormalities that result from pancreatic dysfunction are readily managed by replacement of digestive enzymes in the form of oral medication. Pulmonary infections in these patients are more difficult to diagnose and manage and are often responsible for progressive pneumonitis and death (Fig. 5-7).

Clinical Manifestations

Pulmonary infections in patients with cystic fibrosis are the major cause of morbidity and mortality due to this disease.[217] Although the clinical expressions of the genetic abnormalities are extremely variable, the progression of pulmonary infection is inexorable in most patients. Pulmonary infection is insidious in onset, often manifesting first as persistent, chronic, or intermittent cough following a seemingly routine common cold syndrome in the first year of life. The chronicity of the cough, its accentuation during intercurrent viral respiratory infections, and its progressive nature are important features of this disease. Relative hypoxemia is present early and reflected by an increase in respiratory rate during sleep and, occasionally, dyspnea on exertion. Although initially there are no auscultatory findings, rales and rhonchi become prominent as cough persists and progresses. Some of these patients have wheezing and begin to produce thick sputum. As the pulmonary infection progresses and acute exacerbations become more frequent, the patient develops more copious mucopurulent sputum, thick productive cough, and begins to show the systemic signs of pulmonary insufficiency. These include increased anteroposterior diameter of the chest, clubbing, and shortness of breath.

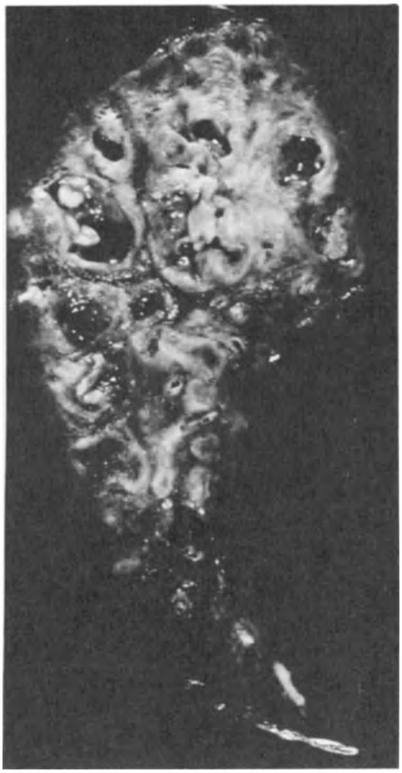

Figure 5–7. Postmortem appearance of lung from a patient with cystic fibrosis and chronic *Pseudomonas aeruginosa* bronchopneumonia. (Courtesy of G. Altshuler, M.D.)

Acute exacerbations in these patients are marked by increased cough, fever, and an increase in the amount and purulence of sputum. Rales and rhonchi become more pronounced and areas of consolidation may be detected radiographically. Air trapping is reflected by hyperresonance on percussion, and wheezing may be prominent in some patients.

Late stages of pulmonary infections include bouts of copious sputum production, breathlessness, hemoptysis, pneumothorax, and pulmonary insufficiency with cor pulmonale. Hypoxemia is progressive throughout the course of the disease and terminal patients often require continuous oxygen therapy.

Although occasional patients with cystic fibrosis develop staphylococcal pneumonia and empyema,[325] bacteremia and the formation of large lung abscesses and empyema are uncommon. Nevertheless, postmortem findings include considerable tracheobronchitis, bronchopneumonia, bronchiectasis, and multiple small peribronchial lung abscesses.

Diagnosis

The diagnosis of cystic fibrosis is confirmed by demonstration of an elevated concentration of sodium chloride in the patient's sweat.[358] The diagnosis may also be suggested by a positive family history, meconium ileus in the newborn, failure to thrive, chronic pulmonary infections, *Pseudomonas aeruginosa* colonization of respiratory secretions, and by azoospermia. The association of pulmonary and gastrointestinal disease is impressive. Many of these features are paralleled by radiographic, microbiologic, and pulmonary function abnormalities.

Initially, the chest X-ray may reveal no changes or slight hyperaeration. These progress to more characteristic air trapping and increased bronchial markings.[358] Later changes include areas of consolidation of an infiltrative variety associated with air trapping and signs of bronchitis. Although the upper lobes are frequently involved, there is no specific radiologic picture. Hypoxemia is detectable early, if it is looked for.

The respiratory microbiologic flora in patients with cystic fibrosis are characteristic.[225] Initially, *Staphylococcus aureus* is the pathogen most frequently isolated from the upper and lower respiratory tract secretions of these patients. The first major pulmonary infection usually involves a respiratory viral infection followed by staphylococcal bronchitis and bronchopneumonia. Once established, *Staphylococcus aureus* is persistently present in the respiratory secretions of these patients, unless specifically treated. *Haemophilus influenzae* and *Pseudomonas aeruginosa* are the other most commonly isolated organisms. Pseudomonas is found most frequently in moderately and severely ill patients, although the presence of *H. influenzae* may not be appreciated due to the fastidious growth requirements of this organism. *P. aeruginosa* is present in 70–90% of patients severely affected with cystic fibrosis lung disease. Both Staphylococcus and *Pseudomonas aeruginosa* are felt to contribute to the pathogenesis of the pulmonary injury through mechanisms of bacterial toxicity and the injuries associated with inflammation and host immune responses.[217] The mucoid nature of *Pseudomonas* in the sputum of patients with advanced disease is very characteristic.

Patients with cystic fibrosis are treated repeatedly and, sometimes continuously, with various antibiotic regimens. Thus, it is not uncommon to culture a variety of Enterobacteriaceae, *Candida albicans*, and aspergillus from their sputum as well.[168] In addition to this, common respiratory viral and mycoplasmal pathogens play important roles in acute exacerbations of pulmonary infection.[257]

Treatment

The treatment of pulmonary infections in cystic fibrosis is far from scientific. There is little doubt that antibiotic therapy has added tremendous benefits to the outcome of acute and chronic pulmonary infections in these patients. However, there are few objective guidelines to rely upon for effective therapy.[217] General principles are as follows.

When pulmonary signs first develop, respiratory cultures usually indicate the presence of *Staphylococcus aureus.* This is generally treated with oral dicloxacillin, cloxacillin, or cephalexin. Because of enhanced clearance of many of these drugs in cystic fibrosis patients,[360] and the need to deliver antibiotic to the sputum of these patients, relatively high doses of drug should be used. For example, 100 mg/kg/day (divided q 6 h) for each of these drugs. This course of therapy is usually continued for 2 weeks and is associated with marked improvement in the patient's clinical status. Some clinicians prefer to continue the antistaphylococcal medication for varying periods of time. Others use these drugs continuously. The next pulmonary exacerbation may be associated with the presence of *P. aeruginosa.* Therapy becomes more complicated, since the effective drugs must be given parenterally and the clinical course may be more prolonged. Currently, piperacillin and tobramycin constitute a popular antipseudomonas therapeutic regimen. Again, increased dosage requirements are noted in these patients[108] (Table 5-13). Newer drugs, such as ceftazidime, azlocillin, and imipenem may also be selected for the treatment of these patients based on in vitro susceptibility studies.[284]

The use of chronic antipseudomonas therapy is not practical, since these drugs must be given parenterally and are generally more toxic than antibiotics effective against *Staphylococcus aureus* and *Haemophilus influenzae.* Nevertheless, such an approach might provide benefit as demonstrated by the efficacy of aerosolized carbenicillin and gentamicin in selected patients.[156]

The value of hospitalization and parenteral antibiotic therapy for the treatment of Pseudomonas pulmonary infections is not always clearcut. Some of the acute pulmonary exacerbactions are clearly due to intercurrent viral and/or mycoplasma infections without significant contribution of *Pseudomonas aeruginosa* to the acute morbidity. It is possible that better guidelines may be provided by periodic quantitative sputum bacteriology in assessing the relative contribution of each pathogen to the infectious episode. This approach, coupled with individualized therapy based on quantitative in vitro susceptibilities and pharmacokinetic monitoring, may suggest the use of more specific antibiotic programs in these patients.

The prognosis for these patients has vastly improved since the 1940s, when survival 1 or 2 years after the initial diagnosis was rare. At present, most of these patients have a life expectancy of 20 years, although the severity of disease is extremely variable. Improved methods for prevention and control of pulmonary infections in these patients will be a major influence in improving their survival.

The general management of these patients is also extremely important. Hence, nutrition, chest physiotherapy, exercise,[366] psychologic support, and genetic counseling are included in modern cystic fibrosis care programs.

TABLE 5–13. Recommendations for Initial Antibiotic Therapy of Acute Pulmonary Exacerbations in Patients with Cystic Fibrosis

Drug	*Sputum Bacteriology*	*Route*[a]	*Dose*
Ampicillin	*H. influenzae* β-lactamase-negative	IM, IV	200 mg/kg/day, divided q 6 h
Amoxicillin	*H. influenzae* β-lactamase-negative	O	100 mg/kg/day, divided q 8 h
Dicloxacillin	*S. aureus*	O	100 mg/kg/day, divided q 6 h
Oxacillin	*S. aureus*	IM, IV	200 mg/kg/day, divided q 6 h
Penicillin G	*S. aureus* non-penicillinase producer *S. pneumoniae*	O, IM, IV	200,000 units/kg/day, divided q 4–6 h
Ticarcillin	*P. aeruginosa*	IM, IV	300 mg/kg/day, divided q 6 h
Moxalactam	*Enterobacteriaceae* *H. influenzae* β-lactamase-positive	IM, IV	200 mg/kg/day, divided q 6 h
Amikacin	*P. aeruginosa*	IM, IV	15 mg/kg/dose q 6 h (adjust peak serum concentration to 15–30 μg/ml; trough to less than 2 μg/ml)
Gentamicin	*P. aeruginosa*	IM, IV	8 mg/kg/day divided q 6 h (adjust peak 4–8 μg/ml; trough to less than 2 μg/ml)
Tobramycin	*P. aeruginosa*	IM, IV	8 mg/kg/day, divided q 6 h (adjust peak 4–8 μg/ml; trough to less than 2 μg/ml)
Chloramphenicol	*H. influenzae* β-Lactamase positive	O, IV	75 mg/kg/day, divided q 6 h (adjust peak 15–25 μg/ml; trough to less than 5 μg/ml)
Trimethoprim-sulfamethoxazole	*H. influenzae* β-Lactamase-positive	O, IV	Trimethoprim 10 mg/kg + sulfamethoxazole 50 mg/kg/day, divided q 12 h

[a] O, oral; IM, intramuscular; IV, intravenous.

Isolation

Spread of pulmonary pathogens in general hospital wards, in camps, and in the community is unusual despite the presence of cough and copious secretions.[300] It seems good sense, however, to protect high-risk patients from the respiratory secretions of cystic fibrosis patients in hospital wards and clinics.

Pneumocystis carinii Pneumonia

Although *Pneumocystis carinii* has been described as a cause of pneumonia in normal newborns[269] and infants,[23] it is predominantly an opportunist. This organism, classified as a protozoan, is an occasional cause of life-threatening pneumonia in immunosuppressed patients, with and without T cell defects,[268] and in those with phagocytic deficiency.[1]

Clinical Manifestations

The oncologist knows full well the clinical picture, characterized by a rapid onset of cough, tachypnea, malaise, dyspnea on exertion, and then at rest. Fever and cyanosis supervene with mortality in almost all patients not receiving treatment. A form of pneumocystosis that attacks predominantly newborns and young infants with malnutrition and other underlying abnormalities has also been described. The course is less fulminant and there is less fever and a lower mortality rate (approximately 50% of untreated infants). This infection may occur together with pneumonia due to cytomegalovirus or chlamydia.[304] This is reminiscent of the association seen between pneumocystosis and cytomegalovirus disease, and candidiasis and Kaposi sarcoma in young homosexuals.[87] Some common immunosuppressive event is probably responsible in many of these cases, but remains to be defined. Combined infections have also been reported in patients after transplantation immunosuppression.

Pneumocystis carinii rarely affects organs outside of the lung, although a few patients have been reported with lymph node[150] and retinal involvement.[193]

Diagnosis

Infantile pneumonia due to *Pneumocystis carinii* demonstrates alveolar plugging with a frothy exudate and interstitial inflammatory infiltration. These pathologic changes are reflected radiographically by mixed alveolar interstitial patterns with some hyperinflation. The chest radiograph in the older patient with Pneumocystis pneumonia is characterized by a more diffuse alveolar pneumonitis with less air trapping. Rarely, the chest X-ray is normal,[295] but the gallium scan may be positive.[202] Unusual radiographic findings include lobar pneumonia, pleural effusions, and pneumatoceles.[211]

Some progress has been made in the ability to grow *Pneumocystis carinii* in tissue culture cells, although the sensitivity and speed of this test preclude its routine use diagnostically.[260] Nevertheless, recent advances in detection of antigen in lung tissue or circulating in the serum offer promise of a more rapid and practical approach to diagnosis.[215, 259] Serologic evidence of antibody against *Pneumocystis carinii* is often nonspecific and may be negative in as many as 50% of infected patients.[274]

Direct visualization of the cysts, sporozoites, or trophozoites (the three forms of the organism that can be seen in vivo) represents the most definite criterion for diagnosis (Fig. 5–8). Specific staining with methenamine silver, toluidine, or giemsa is required.[48] The difficulty lies in obtaining appropriate material for examination. Occasionally, sputum and tracheobronchial brushings may be useful for this purpose. Percutaneous transthoracic needle aspiration provides better specimens; lung biopsy may be necessary in some patients. Experience is necessary in interpreting stained smears as a variety of fungi (Histoplasma, Candida, Cryptococcus, Torulopsis), blood cells, and parasites may be confused with Pneumocystis.[363] The diagnosis depends on a composite of the clinical and radiographic pictures, the nature of the host, identification of antigen or organism and, in some cases, serologic evidence of infection.

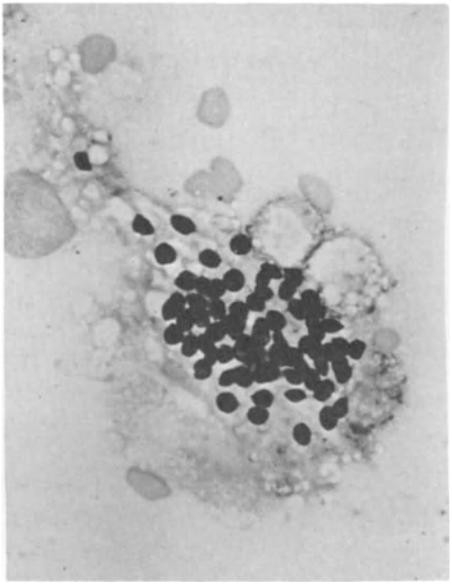

Figure 5–8. *Pneumocystis carinii* demonstrated by Gomori stain of a lung impression preparation. (Courtesy of G. Altshuler, M.D.)

Treatment

The difficulty of confirming the diagnosis often delays treatment in many cases. This is unfortunate, considering the efficacy of trimethoprim-sulfamethoxazole in this condition. Hence, many oncologists prefer to institute this combination early in the development of pneumonitis in the appropriate patient.[159] Assessment of the leukemic child (in relapse or remission) who develops pneumonitis should include a chest X-ray and history, physical examination, and laboratory procedures directed at excluding the common causes of lower respiratory infection. These include pneumococcus, influenza, mycoplasma, Staphylococcus, and gram-negative bacteria (the latter particularly in neutropenic patients). If features suggest pneumocystosis, treatment with trimethoprim-sulfamethoxazole in a dose of 20 mg trimethoprim/100 mg sulfamethoxazole/kg/day should be given for 14 days. The majority of patients will become afebrile and show marked clinical improvement within 3–7 days. Mortality should be less than 20% in treated individuals. Addition of pentamidine to the therapeutic program has no rationale in experimental studies and is not recommended for clinical use.[185] However, failure to improve, or persistence of cysts in lung tissue or tracheal secretions, may indicate resistance to trimethoprim/sulfamethoxazole, and substitution of pentamidine isethionate, 4 mg/kg/day, may be warranted.[333]

Adjuncts to antimicrobial therapy include oxygen to overcome the alveolar capillary blockade characteristic of this syndrome. Occasionally *Pneumocystis carinii* pneumonia may require other adjunctive therapy. This is illustrated by a case of chronic granulomatous disease complicated by this infection.[255] This 11-year-old girl required treatment with granulocyte transfusions as well as with trimethoprim-sulfamethoxazole.

Prevention

Prevention is feasible using trimethoprim-sulfamethoxazole in a dosage of 4 mg trimethoprim/20 mg sulfamethoxazole/kg/day orally (divided q 12 h).[145] However, adverse reactions have been noted in one study in 43/786 patients maintained on this program over a 3-year period;[353] one of these patients died with Stevens-Johnson syndrome. The question then arises when to use this prophylaxis. There is no easy answer. Immunosuppressed populations who have high prevalence rates of *Pneumocystis carinii* pneumonia (as seen in some oncology units) should be handled in this manner. The ambulatory leukemic patient in a population with a low prevalence of this disease probably does not need any preventive antimicrobial. Patients on particularly potent immunosuppressive therapy, those who are malnourished, and those with a previously proven diagnosis constitute the main populations requiring prophylaxis, the latter because of reported recurrences of pneumocystosis after appropriate therapy.[295]

Outbreaks of *Pneumocystis carinii* pneumonia among patients in cancer treatment centers have prompted the use of respiratory isolation techniques for suspected or proven pneumocystosis in such units and in other situations where high-risk patients may be exposed.[294] Experimental evidence of airborne spread supports this recommendation.[158]

Toxocariasis

Epidemiology/Pathogenesis

Toxocariasis is most prevalent in children in the 1–5-year age group, although involvement of the eye is more frequently seen in those above 8 years of age.[283] Dogs and cats are the major animal reservoirs for *Toxocara canis* and *T. catti* in North America. The mature parasite inhabits the gastrointestinal tract of approximately 20% of adult dogs and up to 90% of newborn puppies. These animals excrete eggs in their stools, which then incubate in warm moist soil. After approximately 2–7 weeks of incubation, these eggs become infective for humans. Egg containing soil is probably the most frequent source of human infestation. The eggs mature in the small intestine and often travel to the liver via the portal system. Erosion of blood vessels and entrapment of the larvae in many tissues can occur; however, in most cases, these become walled off and cause no illness. Pulmonary involvement is most frequently noted clinically. This illness is usually mild and self-limited but occasionally leads to serious disease. As expected, the majority of cases in North America are seen in the moist and warm environments of the south central and southeastern United States.

Etiology

Similar pulmonary effects can be induced by either *Toxocara canis* or *T. cati* and can also be caused by ascaris, filiariasis, hookworms, ancylostoma, and capillaria. Many of these are seen most frequently in moist tropical and subtropical areas of the world.

Clinical Manifestations

Syndromes associated with Toxocara and other parasites mentioned above are most frequently manifest by fever, diverse respiratory complaints, and peripheral blood eosinophilia. Bronchiolitis, asthma, pneumonia, or any combinations of these have been noted. Cough, fever, wheezing, and weight loss are frequently noted in symptomatic patients (remember that symptomatic patients represent the minority of those who actually ingest Toxocara). Hepatomegaly is often associated with these pulmonary signs due to invasion of the liver by the larvae; splenomegaly may also be seen. Sometimes there is lymphadenopathy, which may provide a tissue source for diagnosis. There is also a characteristic pruritic eruption in many patients consisting of raised erythematous nodules over the trunk and lower extremities.

When ocular infections occur, it is often the only event noted. This may reflect a different tissue response of the older host or reactivation of infection acquired earlier in life. I favor the latter hypothesis, since the ocular involvement is seen in older children, and associated with marked inflammatory responses suggestive of hypersensitivity.

Diagnosis

Most of the clinical features described above are nonspecific, except for the pruritic rash and eosinophilia. Although serosurveys indicate that up to 54% of North American children have had infection with toxocara by age 8–10 years, very few of these are actually symptomatic.[175] Diagnostic criteria have been suggested for Toxocara infection.[105] These include leukocytosis, eosinophilia > 500 eosinophils/mm^3 or eosinophils > 10% of the peripheral white blood cell count), increase in isohemagglutinins against blood group antigens A and B (this is due to the fact that Toxocara surface antigens cross-react with these human blood group antigens), raised serum immunoglobulin levels (IgM, IgG, IgE, which partly explain the marked hypersensitivity reactions noted), hepatomegaly, and history of soil ingestion. The last feature, pica, is very critical in the pathogenesis of the condition and in suggesting the diagnosis.

Radiographic changes usually include transient pulmonary infiltrates, but these are only present in approximately one-half of the patients with pulmonary signs.[283] The diagnosis is confirmed by demonstration of Toxocara larvae in tissue specimens obtained from lung, lymph node, or other involved organs. Diagnosis can also be made by demonstration of seroconversion or a titer of at least 1:32 by the ELISA test, which is at least 70% sensitive and over 90% specific for this infection.[34] Although eosinophilia is suggestive, it may persist for months to years after the original infection.

Therapy

The vast majority of cases are self-limited and benign. When pulmonary disease is prominent or progressive, diethylcarbamazine or thiabendazole can be used.[46] Steroids have also been recommended for severe pulmonary disease, mycocarditis, and active choreoretinitis.[33]

Prognosis

Pulmonary infection is usually self-limited within 2–6 weeks but persistent cough, malaise, and pruritic skin eruptions may warrant chemotherapy. The occasionally fatal cases reported in children are due to myocarditis, central nervous system infection, or severe pneumonia.

Prevention

Since ingestion of soil contaminated with Toxocara eggs is the most important mechanism of spread, methods need to be devised to keep children away from such soil or to keep dogs and cats away from these areas, or both. The immunocompromised host, the patient ingesting a large inoculum, and unknown factors seem to contribute to the occasional case that develops toxocara pneumonia or other serious organ involvement. Transient immunosuppression may allow larvae to erode through blood vessels and manifest ocular involvement some time after the original infection. Since chemotherapy is far from efficient, methods for prevention should be given priority. These are best translated in public health terms by hygienic and animal control policies.

Histoplasmosis

Pulmonary histoplasmosis has many features in common with tuberculosis. The majority of patients infected develop immunity characterized by skin hypersensitivity and humoral antibodies, and are asymptomatic. As in tuberculosis, their initial infectious episode may be completely symptom-free or indistinguishable from an upper respiratory infection.[129] The risk of dissemination is increased in all ages in immunosuppressed patients, including leukemics, steroid-dependent asthmatics, and debilitated hosts.[74]

Epidemiology

Some of the epidemiologic characteristics of histoplasmosis differ from tuberculosis. Many of the reservoirs are well-defined, *Histoplasma capsulatum* being particularly prevalent in chicken houses and bat caves. Bird and bat droppings are often contaminated and, in favorable environmental conditions (such as seen in the Mississippi and Ohio Valleys of Central United States), Histoplasma mycelia abound. Outbreaks of histoplasmosis have been reported in pigeon breeders, spelunkers (bat cave explorers), and in urban populations living close to large construction projects that raise clouds of fungus-containing dust. This was seen in the 1960s in Montreal during construction of the subway system and, more recently, in a large urban renewal construction program in Indianapolis.[351] In the latter outbreak, seroepidemiologic studies estimated 120,000 individuals were infected. Four hundred and eighty-eight cases required medical attention and 60 were disseminated. This experience provides the most recent estimate of infectiousness and expression of disease in urban-acquired histoplasmosis. Elderly patients, immunosuppressed patients,[352] and those exposed to high inocula seemed at highest risk for dissemination.[351]

Clinical Manifestations

The usual incubation period of histoplasmosis is estimated to be 3–30 days. The route of infection is predominantly respiratory, although a few cases of cutaneous,[73] and a case of venereal inoculation have been documented. The majority of patients are either asymptomatic or have a mild influenza-like syndrome. Among the latter, fever and headache are consistent signs, and substernal pain, cough, and chills are seen in about two-thirds of cases. Some children may manifest vomiting and diarrhea as well. These signs and symptoms are generally self-limited within 1 week in many cases and 3 weeks in almost all. Rare presentations include parotitis, cervical lymphadenitis, mediastinal mass, pericardial effusion, pulmonary infarction, aseptic meningitis, and hemolytic anemia.[346]

Dissemination is heralded by persistent signs and symptoms, hepatosplenomegaly, weight loss, persistent fever, cough, and, occasionally, erythema nodosum.[130] Later manifestations are referable to extrapulmonary complications (polyarthritis or arthralgia may be prominent signs as well). Reinfection and reactivation may also occur and the manifestations are similar to primary pulmonary infection.[266]

Diagnosis

The diagnosis of histoplasmosis may be inferred during an outbreak situation, or when the patient's occupation or avocation relate to birds or bats. Rarely, laboratory exposure may provide the clue. Physical examination and laboratory tests will be nonspecific in the first few weeks of illness, although demonstration of the yeast and/or its culture may be possible in respiratory secretions or skin lesions, depending on the clinical manifestation of the infection. Only about 20% of children with histoplasmosis will demonstrate pulmonary infiltrates. These are generally perihilar and are mild and self-limited. Some hilar lymphadenopathy may also be prevalent, perhaps explaining the substernal pain and discomfort noted by many patients. There is rarely a need to investigate patients within the first 3 weeks of appearance of symptoms, since histoplasmosis seldom requires therapy at this stage. Nevertheless, consideration of the diagnosis should prompt obtaining serum that can be used later as a reference for confirming the diagnosis.

Skin testing with histoplasmin is generally not recommended. Although a 1:100 histoplasmin skin test of at least 8 mm induration at 48 h is considered diagnostic by some investigators, others describe frequent false-positive reactions. It is also estimated that 10–50% of skin tests will influence the patient's serologic response. Since the confirmation of initial infection and evidence for dissemination depends partly on serial demonstration of changes in complement-fixing antibodies, skin testing may create diagnostic difficulties. Recent experience with a yeast lysate preparation skin test suggests that this product, if standardized, may be useful because of its lack of effect on serologic markers.[203] Coccidioidin skin test material can also boost serologic immunity to histoplasmin and should be avoided.

Demonstration of a fourfold rise in complement-fixing antibody, or a conversion from negative to positive serology, is confirmatory of infection. Both yeast and mycelial antigens can be used. Immunodiffusion tests can also be interpreted in this way. Dissemination beyond the pulmonary system and reactivation are often indicated by a continuing rise in antibody.

Granuloma containing organisms resembling *Histoplasma capsulatum* are sometimes visible in bone marrow or liver biopsy specimens, or from specific lesions (e.g., skin, gastrointestinal tract).

The diagnosis of histoplasmosis is confirmed by culture of the yeast. Although the mycelial form is commonly seen in nature, the yeast form is the one encountered at mammalian body temperatures. Unfortunately, Histoplasma grows poorly in anaerobic blood cultures, a fact that should be kept in mind when looking for fungemia.

Therapy (Table 5-14)

Most patients with acute acquired histoplasmosis spontaneously recover within 2 weeks, and therapy is not required. When histoplasmosis is acquired in the first year of life and/or in patients with other predisposing conditions, early therapy with amphotericin B may be lifesaving. Decisions about the timing of therapy are difficult because of the toxicity of amphotericin B and the necessity for hospitalization.

There is some debate about the indications for therapy with amphotericin B in early stages of histoplasmosis and in isolated pulmonary disease. Although rare, pleural effusion or cavitation should be treated.[348] When pulmonary disease is prolonged beyond 2–3 weeks, therapy is also probably useful. In such cases, a 1–2-week course of therapy may suffice, although specific guidelines for duration and dose are not readily available.[113]

Some of the dilemmas about therapy may be resolved if early experience with ketoconazole, an oral antifungal agent, is confirmed.[296] One recent case report, however, attests to the peculiar host/parasite relationship in this infection as well as the difficulty of effective antifungal therapy.[147] In

TABLE 5–14. Classification of Histoplasmosis

Pulmonary histoplasmosis, acute; normal X-ray	In 80%: influenza-like or no illness; self-limited in less than 1 week
Pulmonary histoplasmosis, acute; abnormal X-ray	In 19%: pulmonary infiltrate with or without hilar lymphadenopathy; self-limited in 2–3 weeks
Pulmonary histoplasmosis (chronic)	In less than 1%; progressive pulmonary and systemic signs; treatment is short course (1–2 weeks) of amphotericin B or oral ketoconazole × 4 weeks
Disseminated histoplasmosis	Persistent fever, systemic and focal signs, usually in immunocompromised hosts; long-term therapy (greater than 6 months) may be required.
Localized histoplasmosis (rare)	Surgery and short-term therapy may be curative. Ketoconazole trial warranted. Must rule out disseminated infection.
Reinfection pulmonary histoplasmosis	Second episode of pulmonary infection in patient exposed to high inoculum; for treatment see pulmonary chronic (above).
Reactivation histoplasmosis	Can be seen in immunocompromised patients years after primary infection; for treatment see disseminated (above).

this case, an adult patient with disseminated disease was treated with ketoconazole for a year. This was followed by relapse with culture of viable organisms from an abdominal aneurysm.

Extrapulmonary Histoplasmosis

As discussed above, extrapulmonary histoplasmosis occurs most frequently in immunosuppressed individuals and may be expected with some increased frequency in the first year of life. Adrenal corticosteroids and leukemia seem to be particularly important predisposing factors. Almost every organ and tissue in the body has been involved in such infections and miliary disease can be seen. The fact that this is not always severe is witnessed by the occasional observation of miliary calcifications in chest X-rays taken in asymptomatic subjects. Since calcifications usually occur in 1–7 years after histoplasmosis, it is often difficult to pinpoint the clinical event associated with the primary infection. Among the manifestations of disseminated disease noted, erythema nodosum, adrenal insufficiency, and disseminated intravascular coagulation in the acute stage are of particular note.

A variant of histoplasmosis is seen in Africa, where the predominant form is a localized chronic skin, subcutaneous tissue or bone lesion, or a rapidly disseminating disease due to *Histoplasma capsulatum* var. *duboisii.*[289] Pulmonary disease is rarely seen in this condition.

Since the mycelial form is most infective but not present in man, human-to-human spread is unlikely. Isolation and control measures are not required in hospital but avoidance of bird roosts and heavily infected soil and other preventive measures may be important to limit spread of disease in the community.

Coccidioidomycosis

Acute Self-Limited Infection

Pulmonary infection is the most frequent manifestation of coccidioidomycosis in man. Fungal arthrospores are present in the soil and plant products in many regions of the southwest United States, where skin test results indicate that approximately one-half of children experience infection with this organism by 4 years of age, and three-quarters by puberty.[84] Nevertheless, at least two-thirds of those who inhale this fungus have no symptoms at all. Of the remaining one-third, 60% experience a "flu-like" syndrome characterized by fever, chills, myalgia, cough and, occasionally, pleuritic pain or arthralgia.[18] There may be a morbilliform, scarlatiniform, erythema nodosum, or multiforme rash associated with these symptoms. Patients with this condition may also have pulmonary infiltrates and hilar adenopathy, or a normal chest X-ray. The infection is self-limited within 2–3 weeks in at least 60% of symptomatic subjects.

Progressive Pneumonia and Disseminated Infection

A small percentage of patients go on to develop chronic or progressive pulmonary disease characterized by pulmonary infiltrates, chronic cough, weight loss, fever, and malaise.[85] This condition, and disseminated infection, require antifungal therapy. Disseminated disease is most frequently manifest by skin, subcutaneous tissue, bone, or central nervous system involvement.[176] Dissemination is most likely to occur in pregnant or immunocompromised patients.[213]

Diagnosis

The diagnosis of coccidioidomycosis is made by the appropriate epidemiologic history (sometimes a very brief exposure to the endemic area is sufficient) and a compatible clinical syndrome. The usual incubation period between inhalation of the fungal spores and respiratory symptoms is 7–21 days. However, disseminated disease can occur at any time after pulmonary infection (or, occasionally, without a pulmonary component).

Coccidioidin and spherulin skin tests generally become positive between 1 and 6 weeks after the appearance of the first signs of pulmonary involvement.[120] Unfortunately, false-negative results may occur in as many as 50% of patients with microbiologically proven infection. The skin test characteristically becomes negative and is least useful in patients with extrapulmonary infection. In those patients, a rising titer of complement-fixing antibody is more suggestive of disease.[84] The presence of this antibody in cerebrospinal fluid is diagnostic of coccidioidal meningitis. Microbiologic culture from infected tissue and secretions confirms the diagnosis. Eosinophilia is commonly present, particularly in patients with erythema nodosum, but is a nonspecific sign.

Once pulmonary signs continue beyond 8 weeks, it is likely that chronic progressive pulmonary disease is occurring. This has the gravest prognosis in children under 5 years of age, and in elderly and immunocompromised patients.

Treatment

Treatment of pulmonary coccidioidomycosis depends on the use of amphotericin B, although recent experience with oral ketoconazole has been promising.[311] In any event, treatment may require administration of antifungal drugs for 6 months to 2 years.[85] This therapy is guided by microbiologic and clinical criteria, and intensive and long-term followup is necessary. In most cases the prognosis for pulmonary infection is good. The outcome of disseminated disease is less bright, with mortality rates as high as 50% reported for cases of coccidioidal meningitis. Combined surgical and medical approaches are useful in patients with cutaneous, subcutaneous, and osseous manifestations.[85]

Person-to-person spread is not reported, although newborns can acquire infection from genitourinary lesions in the mother.[31] Furthermore, spores present in cultures pose a serious risk to laboratory workers.

Legionellosis

Epidemiology

Legionella pneumonia was first recognized in adults in the community and then, more frequently, in immunocompromised hospitalized patients.[229] It is rare in normal[233] or immunocompromised children, although serologic evidence of experience with Legionella or Legionella-like antigens was noted to develop in 52% of young children (under the age of 4 years) during a 5-year surveillance.[6] Some estimates suggest that

Legionella is involved in 1–2% of pneumonias in normal children, but the evidence is predominantly serologic in nature.[247] Infection has been reported in all ages, even in a 4-month-old with pneumonia.[248]

Etiology

There are seven recognized species of *Legionella (pneumophila, bozemanii, dumoffii, gormanii, jordanis, longbeachae,* and *micdadei*).[229] *Legionella pneumophila,* in addition, is divided into six serogroups, and is the originally described and most frequent cause of legionellosis. The other species of Legionella may be just as virulent, as witnessed by a fatal case of pneumonia due to *dumoffii* species in an 18-year-old with lupus erythematosus.[144]

Clinical Manifestations

The major manifestation of legionellosis is pneumonia. Occasionally, cases are reported that are indistinguishable from bronchiolitis or bronchitis, and even lung abscess[338] and cavitary disease[226] have been described. The majority of cases, however, come to attention because of the presence of cough and fever of rather acute onset, often associated with encephalopathic signs, hematuria, and rises in SGOT. These signs are less common in children. There are less upper respiratory signs and more abdominal discomfort and diarrhea than noted with classic causes of pneumonia. The physical examination reveals moist rales in most patients, although rhonchi are often present as well.

The radiographic appearance of Legionella pneumonia is not distinct, and patchy infiltrates, segmental consolidation, hilar enlargement, and peribronchial thickening have been noted. An interstitial component is often present as well. Pneumothorax[318] and empyema, with a predominance of polymorphonuclear leukocytes, has also been described.[233] The clinical features of Legionella pneumonia are derived mainly from experience in adults, although pediatric cases are being noted more frequently.

Extrapulmonary manifestations are not uncommon. For example, the liver and brain were infected with Legionella in a recently reported fatal case of pneumonia in a 5-month-old child with severe combined immunodeficiency.[77] Interestingly, this patient also had parainfluenza 3 and *Pneumocystis carinii* present in the lungs. A perirectal abscess due to *Legionella pneumophila* and anaerobic bacteria has also been reported.[9]

Diagnosis

Legionella pneumophila and other Legionella species can be cultured from the sputum and lower respiratory tract secretions (and, occasionally, pleural fluid or other tissues) by use of modified agar.[91] It can also be demonstrated in these specimens by fluorescent staining. Infection was recently reported in a child with Down's syndrome, where the diagnosis was made by culture of the organism from the respiratory secretions as well as demonstration of *Legionella pneumophila* antigen in the urine.[316] Currently, the majority of cases are diagnosed by serologic means; however cross-reactions with mycoplasma[29] and anaerobes, including Bacteroides,[90] have been noted. Since the majority of seroconversions in children have been reported in the absence of clinical signs, the possibility of cross-reactive antigens or asymptomatic infection must be kept in mind.

Therapy

Erythromycin is the most active drug in vitro and in vivo against Legionella species.[355] Usually, a 3-week course of erythromycin is necessary. Rifampin and sulfonamides are also active. Appropriate decontamination procedures to eliminate Legionella from water sources are important in the control of spread. Person-to-person transmission is unlikely under normal conditions, but could occur via contaminated respirator equipment and fomites.

Prognosis

Despite 3 weeks of therapy, relapses have been noted.[278] This is particularly likely to occur in immunocompromised patients. Pulmonary fibrosis has also been noted long after recovery from Legionella pneumonia.[37]

Although *Legionella pneumophila* is probably a rare cause of pneumonia in normal children, refinements in diagnosis should reveal the true spectrum of this illness. At present, it should be considered early in immunocompromised patients and in other children with progressive pneumonia associated with encephalopathy and hematuria. Clinical response to therapy is often dramatic within 24–48 h.

Nocardiosis

Epidemiology

This is a rare cause of pulmonary infection in children and adults that can disseminate to almost every organ of the body.[76] The disease is usually seen in immunocompromised patients, in whom the lung is most frequently involved; however, infection of the central nervous system and skin may also occur. In a recent survey of 21 cardiac transplant patients 81% had only lung involvement.[292]

Etiology

Nocardia pulmonary lesions are usually caused by *Nocardia asteroides*, whereas *Nocardia brasiliensis* and *Nocardia caviae* usually cause focal mycetoma of the skin and subcutaneous tissues. The latter are seen in normal patients, often associated with skin trauma.[197]

Clinical Manifestations

Pulmonary disease due to Nocardia is usually chronic in nature and consists predominantly of focal pneumonitis.[76] Occasionally, the onset can be acute with dissemination to the brain and other tissues. The more debilitated the host, the greater the risk of this complication. Chronicity of several months' duration is the hallmark of both pulmonary and extrapulmonary lesions.

Diagnosis

The diagnosis rests on demonstration of gram-positive and partially acid-fast bacilli in tissue, and culture of the organisms. There is no adequate serologic or skin test. Patients who are immunocompromised and have focal lesions require aggressive diagnostic approaches, including early lung biopsy, to establish this diagnosis. Rarely, the organism can be cultured from the blood. This usually means disseminated disease. Culture of Nocardia from the upper respiratory tract is not necessarily synonymous with infection, but should not be discounted as a contaminant in the appropriate host.

Therapy

Therapy of nocardiosis is complicated by the fact that the hosts are often severely immunocompromised. The more immunodeficient the host, the less likely therapy will be effective. Nevertheless, a combination of surgical and medical therapy is often efficacious. Sulfonamides alone, or in combination with trimethoprim, remain the most active drugs with the most favorable clinical experience.[297] Patients with isolated pleural and pulmonary lesions seem to have the best prognosis.[117] An analysis of 78 cases of systemic nocardiosis demonstrated a favorable outcome in 37 of 39 cases with only pulmonary disease.[117] There were no deaths in those treated for longer than 6 months, and no difference in outcome between patients treated with medical therapy alone vs. those treated both medically and surgically.

There are no prospective controlled studies to support the theory that trimethoprim/sulfamethoxazole may be superior to sulfonamides alone, but favorable experience with the combination is increasing.[297] Whichever drug is chosen, long durations of treatment and followup are required. In fact, one patient was recently reported to relapse even after 6 months of treatment with the combination of trimethoprim/sulfamethoxazole and surgery.[118] An average of 13 months of sulfisoxazole was used in another study,[292] however one patient relapsed three times (once 39 months after a year's treatment!).[315]

Alternate drug therapy for nocardiosis might include minocycline[256] or amikacin.[361] In vitro susceptibility studies are technically difficult, but may provide useful guidelines in such cases.

These studies are retrospective and consist of a heterogeneous population of patients. Much depends on the state of immunity, nutrition, and age of the host. Concurrent infection with other opportunists may also contribute to the difficulty in diagnosis and management of these cases. For example, a peculiar association of nocardiosis with subsequent nontuberculous mycobacteria has also been reported.[291]

Blastomycosis

Epidemiology

Blastomycosis is a rare disease of children that can be treated effectively.[307] It is seen most frequently in the United States in farmers, forestry workers, and in those exposed to soil and pigeon droppings. One case in a 3-month-old, occurred after exposure to blastomycosis in a pet dog.[64] In another, intrauterine transmission was responsible for fatal blastomycosis

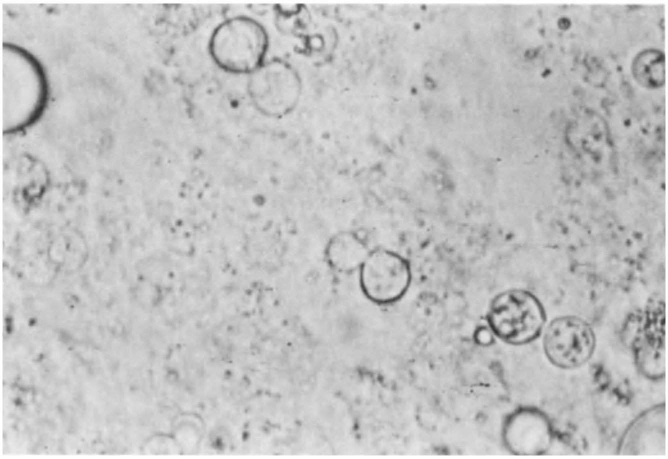

Figure 5–9. Spores of *Blastomyces dermatitidis*.

in a 3-week-old.[345] The disease has been reported mainly from the southern and Great Lakes regions of the United States, as well as in South America and Africa.[281] Most of the hosts are immunologically normal, but the infection can be opportunistic as well.

Etiology

Blastomyces dermatitidis is a dimorphic fungus that grows in the mycelial phase at room temperature, at which time it produces spores (Fig. 5–9). Inhalation of these spores produces predominantly pulmonary disease in humans, during which the spores take on the yeast form at body temperature. Disseminated disease can occur as well. Paracoccidioidomycosis (South American blastomycosis) is due to *Paracoccidioides braziliensis,* similar in nature to blastomycosis, and extremely rare in children.

Clinical Manifestations

The disease resembles tuberculosis and histoplasmosis in many respects and pulmonary, skeletal, and skin lesions may be present.[307] The condition can present as acute or chronic pulmonary disease and should be suspected in children in appropriate geographic areas with pulmonary infections that do not quickly resolve.[196] The disseminated form most frequently manifests as skin nodules or ulcers, but infection can also involve bone and the male genitourinary tract.[281]

Diagnosis

The diagnosis is made most accurately by demonstrating budding yeast cells with double refractile walls in the sputum or upper respiratory secretions of patients with pneumonia. These can also be seen in skin lesions and in biopsy specimens taken from other sites. Occasionally these yeasts are confused with pollen or red blood cells. A sputum stain or 10% KOH smear will usually reveal the presence of these organisms.[334]

The diagnosis can also be suggested by a fourfold rise or a single high titer in a double-immunodiffusion antibody test. However, the diagnosis is not ruled out if the test is negative.[354] A skin test can also be used, but is much less reliable. Appropriate microbiologic cultures from sputum and other infected tissues are the sine qua non of diagnosis.

Therapy

Amphotericin B is the drug of choice. There is some debate as to whether benign, self-limited, pulmonary conditions exist that may not require therapy.[270] In any event, the recommended total dose of amphotericin B is approximately 30 mg/kg over a 3–4-week period. The drug can be given three times a week after initial clinical stabilization. Shorter courses of drug may be possible in some children with mild disease.[64] Ketoconazole has been useful in some patients with paracoccidioidomycosis.[271]

Prognosis

The disease can be effectively treated if diagnosed early. Some patients, despite appropriate antifungal therapy, develop persistent mild obstructive airway disease. This has recently been demonstrated in three of 14 children who had radiographic and pulmonary function abnormalities months to years after their initial episode of blastomycosis.[264] This disease is rare, and, like tuberculosis and histoplasmosis, has diverse clinical manifestations. It can be fatal and should be thought of in selected cases with persistent pneumonia.

Cryptococcus

Despite the fact that this infection is acquired by inhalation of *Cryptococcus neoformans,* the primary manifestation is usually meningitis (Chapter 9). Pulmonary involvement is generally short-lived and asymptomatic, except in immunosuppressed or other high-risk hosts.[92] An illustrative case is reported in a 14-year-old boy with pulmonary alveolar proteinosis.[317] The presence of interstitial pneumonia in an abnormal host should suggest the possibility of Cryptococcus. Diagnosis can be confirmed by lung biopsy (direct visualization of yeast in tissue and fungal culture) or by the demonstration of cryptococcal antigen in the patient's serum, in the absence of serum rheumatoid factor.[110] Cryptococcus is extremely rare in children and should be considered only in immunosuppressed patients and in those frequently exposed to pigeons.

Sporotrichosis

Sporotrichosis is usually manifest as a lymphocutaneous infection (Chapter 7). Pulmonary sporotrichosis is rare in adults and even more so in children. The disease resembles tuberculosis in many respects and is caused by inhalation of *Sporothrix schenckii,* a ubiquitous fungus in temperate and tropical countries. The diagnosis rests on microbiologic culture, although serologic evidence of infection can also be obtained. Treatment is extremely difficult, consisting of saturated solution of potassium iodide for 3–6 months. Patients do less well when treated with amphotericin B, since several have relapsed after such therapy or after treatment with hydroxystilbamidine and miconazole.[234]

Infrequent Causes of Pneumonia

Actinomycosis

Actinomyces israelii is the most frequent of the four species of Actinomyces that can cause suppurative infections in man; however, all are rare in children.[308] These infections are uncommon and generally cervicofacial or abdominal in location. When a pulmonary or mediastinal lesion is associated with sinus formation, or persistent empyema, Actinomyces should be considered in the differential diagnosis. Some of these children have a history of dental or oral infections. Two recent cases indicate the spectrum of disease can be protean, one child having an asymptomatic left upper lobe mass and the other, chronic back pain, weight loss, amenorrhea, and a posterior mediastinal mass.[302]

The diagnosis of actinomycosis is made by culturing this anaerobic bacteria from the lesion.[305] Sometimes it may be associated with *Actinobacillus actinomycetemcometans,* producing a mixed aerobic/anaerobic infection. Treatment consits of penicillin or erythromycin for as long as 12–16 months. Surgical drainage may reduce morbidity and shorten the need for such prolonged therapy. Other manifestations of actinomycotic infections are summarized in the references.

Mucormycosis

Pulmonary mucormycosis is rare in adults with predisposing malignancies and poorly controlled insulin-dependent diabetes mellitus.[200] A fatal case was recently described in a 14-year-old diabetic.[169]

Aspergillosis

Pulmonary aspergillosis is rarely noted in normal patients in the pediatric age group; however, these infections have been noted with increasing frequency in children with cystic fibrosis, asthma, chronic granulomatous disease,[67] and other predisposing immunodeficiency syndromes. *Aspergillus flavus* and *Aspergillus fumigatus* are common air contaminants and may be particularly associated with use of air conditioners or during room construction.[282]

Pulmonary aspergillosis is divided into three major categories: invasive, allergic bronchopulmonary, and saprophytic. The saprophytic form generally present as a fungus ball, or aspergilloma, usually in preexisting cavitary lung lesions.[126] Aspergillus colonizes the cavity and forms a circular lesion visible on X-ray, and is often associated with hemoptysis. Patients develop precipitating antibodies to Aspergillus antigens and may have chronic cough. The treatment is surgical in most cases, as systemic antifungal therapy has little effect.

Invasive aspergillosis may be seen in patients with malignancies or immunodeficiency syndromes. Corticosteroid use in transplant patients seems a very important predisposing factor.[137] The diagnosis is suspected when this organism is repeatedly cultured from respiratory secretions, although antibodies against Aspergillus may indicate the presence of this infection as well.[111] More recently, Aspergillus antigen has been detected in the sera of such patients.[347] The treatment of invasive aspergillosis is difficult, since these infections are often seen in patients with serious underlying conditions and antifungal drugs have limited efficacy. Recent experimental experience with high-dose ketoconazole therapy has been encouraging.[148]

Bronchopulmonary aspergillosis is usually manifest by cough, eosinophilia, and wheezing, often in asthmatic patients. Other inhaled fungi may also be responsible.[122] The condition is best treated by the administration of corticosteroids. Invasive disease should be ruled out in such patients and corticosteroid therapy interrupted once host-immune defences adequately control growth of the organism.

Melioidosis

Melioidosis should be considered in patients from Southeast Asia who have a subacute or chronic course of fever, cough, weight loss, and a negative tuberculin test.[254] Chest X-ray may show upper lobe infiltrates, cavitation, and atelectasis. Although any organ in the body may be involved by *Pseudomonas pseudomallei*, the causative agent of melioidosis, the lung is the most frequently affected.

Culture of the bacteria from the sputum and, occasionally, the blood or other tissues, is confirmatory.[288] Seroconversion documented by a fourfold change in hemagglutination titer is also useful.

Treatment of acute melioidosis should be prescribed for at least 4 weeks after diagnosis; chronic forms should be treated for approximately 6 months. Chloramphenicol combined with kanamycin or amikacin is most often used. Chloramphenicol and tetracycline can also be used in patients over 7 years of age. Since the latter program can be administered orally, it is often preferred for prolonged therapy. The prognosis is good, although some patients may require surgical intervention.

Q Fever

Epidemiology

This rickettsial infection is usually acquired by inhalation of dust contaminated with excreta from sheep or cattle, the apparent source of infection in several large outbreaks in biologic research centers.[141] Urban populations, however, may also be at risk.[277] The infection is rare in the pediatric age group.

Etiology

The rickettsia *Coxiella burnetii* is the cause of this infection and is highly infectious in the laboratory and in nature,[14] so much so that attempts at culturing the organism are not usually recommended.

Clinical Manifestations

Most subjects who inhale these pathogens remain asymptomatic or suddenly experience a "flu-like" illness, with fever, myalgia, and headache. The headache can be severe and associated with neck stiffness, although there is no objective evidence of meningitis upon examination of the cerebrospinal fluid.

Approximately one-third of those infected develop patchy pulmonary infiltrates, although cough may be present in the majority of patients. Liver abnormalities (usually elevated cellular enzymes SGPT, SGOT) are often detectable, but clinical jaundice is unusual.

Diagnosis

The epidemiologic history provides the most substantial clue to the diagnosis. The complement-fixation test rises to at least four times the acute serum titers within 2–3 weeks. Persistence of this antibody titer for up to 2 years may occur and should not be taken as evidence of disseminated disease or endocarditis. Rather, an elevated antibody to the "phase I" antigen should be used to confirm the latter diagnosis.[173]

Therapy/Prevention

Those who have dealt with the treatment of chronic Q fever endocarditis so fear this complication, that they recommend tetracycline or erythromycin therapy for at least a 2–3-week period for all infected subjects.[220] Development of a vaccine may be useful for high-risk subjects.[10]

Prognosis

The infection is usually inapparent in children. Even when pneumonia is present, a favorable outcome should ensue within a few weeks after initiation of appropriate antibiotic therapy.

Parasitic Pulmonary Diseases

Some of the parasitic causes of pulmonary infection are listed in Table 5–15. One of these, paragonimiasis, has recently been seen more fre-

TABLE 5–15. Lower Respiratory Infections Due to Parasites

- *Entameba histolytica*
  - Usually in right lower lobe by direct extension from hepatic abscess
- *Paragonimus westermani*
- *Echinococcus granulosus*
- *Ascaris lumbricoides*
  - Hypersensitivity
- *Strongyloides stercoralis*
  - Pneumonitis with or without eosinophilic granuloma
- *Wucheria bancrofti*
- *Trichinella spiralis*
  - Hemoptysis, eosinophilia

quently in the Western world coincident with increases in immigration from endemic countries.[45]

Paragonimiasis

Epidemiology Paragonimiasis is prevalent in Southeast Asia, the Philippines, and in the Far East, but there are also endemic foci in South America and Africa.[340] The ova are encysted in fresh water crabs and crayfish which can be ingested by man. The cysts mature in the upper gastrointestinal tract, and the worm penetrates through the intestinal wall into the peritoneal cavity and then through the diaphragm into the lung. The worms then lay ova that are coughed up and swallowed. These ova are then excreted into the waters where they reenter the intermediate hosts that can be further ingested by man. Thus, direct man-to-man spread is not seen.

Clinical Manifestations Most cases of pulmonary paragonimiasis (the most frequent clinical expression of infection is with *Paragonimus westermani*) resemble tuberculosis.[170] Thus, there is hemoptysis, chronic cough, and even clubbing. Fever is unusual, although it may be associated with pleural effusion and atelectasis. Atypical presentations include acute abdominal pain suggestive of appendicitis and asymptomatic cavitary disease.[340]

Diagnosis. A clinical picture resembling tuberculosis in a child with negative tuberculin skin test from any of the endemic regions mentioned above should suggest the diagnosis. The clinical picture is variable. Pulmonary findings include interstitial infiltrates, cystic areas, and hilar adeonpathy. There is peripheral eosinophilia as well. The definitive diagnosis is made by finding the ova of *Paragonimus westermani* in the stools, sputum, or tissues of the patients.[45] Visualization of the worm in pulmonary tissue would also be diagnostic, but is, fortunately, a tissue not frequently available. There is a complement-fixation test that can be an adjunct to the diagnosis, but its specificity and sensitivity are limited.

Treatment

Mortality associated with pulmonary paragonimiasis in normal children is infrequent, although the disease can be debilitating and may require 5–10 years for natural resolution. Because of this, and the danger of pulmonary bleeding and rare (but fatal in up to 25%) spread to the central nervous system and skin, treatment is recommended. Traditionally, this has been carried out by the use of bithionol 50 mg/kg given every other day for 15–30 doses. More recently, praziquantel 60 mg/kg, divided three times a day, for 2 days, has been used successfully.[303]

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6

Gastrointestinal Infections

Gastroenteritis

Gastrointestinal infections are second only to respiratory infectious diseases in frequency and morbidity. A conservative estimate places the annual worldwide mortality from gastroenteritis-related infections at six million children. Although stomatitis and esophagitis are occasionally seen as distinct entities, the vast majority of gastrointestinal infections manifest as vomiting and/or diarrhea syndromes, commonly referred to as gastroenteritis. In many cases the term "enterocolitis" describes the pathologic and clinical features more accurately.

Epidemiology

Diarrhea is most pronounced in communities where undernutrition, poor hygiene, and poorly developed community facilities for sewage and drinking water exist. In such communities, as recently described for Bangladesh, the peak incidence of diarrhea syndromes occurs between 2 and 11 months of age, and most infants in their first year of life can be expected to have seven episodes of gastroenteritis.[38] Expression and frequency of infection are related to decreased host resistance secondary to nutritional deficiencies, and increased spread referable to crowded living quarters, contaminated water and food, inadequate washing and toilet facilities, abundant flies, and inadequate refrigeration and cooking technology.

Young infants are most prone to the dehydrating and debilitating effects of acute gastroenteritis and have the highest attack rates. Some organisms, such as Shigella, predominate in the summer and fall months, whereas others, such as rotavirus, are frequent in the winter months in temperate climates[53] and year-round in the tropics.[38] Campylobacter and enterotoxigenic *E. coli* are also very prevalent in such areas.[94]

In developed countries, diarrhea outbreaks occur in day-care centers[297] and other institutions, as well as in the community.[261] Here the same problems of hygiene, crowding, frequent direct contact, and inappropriate disposal of waste contribute to the scope of the problem. In North America, such outbreaks are most frequently seen in infants under 2 years of age, and in large day-care centers or in those that place less emphasis on space, hygiene, and adequate numbers of staff. The most virulent organisms (i.e., those that can cause disease with the smallest inoculum) are frequently responsible. These include Shigella, Giardia,[347] and rotavirus, and are also among the most frequent gastrointestinal pathogens worldwide. Rarely, *C. difficile* may be causative.[197]

Many mechanisms of spread may be involved. For example, Norwalk virus may be foodborne, waterborne, or spread from person to person.[186] In fact, two of these mechanisms were involved in an outbreak after exposure occurring in a swimming pool.[187]

Pathogenesis

Host factors important in the pathogenesis of gastroenteritis include young age, wasting (i.e., low weight in relation to height), and poor hygiene. In addition to frequency, the duration of illness is also increased in malnourished children.[385] The interplay of nutrition and infection is a remarkably constant feature in the pathogenesis of gastroenteritis and its complications. Patients with reduced stomach acid secretion are also at increased risk for salmonellosis and toxigenic diarrheas.[268]

Acquired immunity to gastrointestinal infections is often very specific for the individual serotype of bacteria or strain of virus, and can be quite short-lived. For example, gastrointestinal immunity provided by breast milk is often effective, probably due to its content of secretory IgA, but is not expected to last beyond the breast-feeding period.[61] Both humoral and secretory immune mechanisms are usually involved in recovery from enteric infections but their respective roles in prevention are not completely understood.

Characteristics of the infecting organism also play important roles in the pathogenesis of infectious diarrhea. The major pathogenic mechanisms described include adherence (i.e., the ability of the pathogens to attach to the gastrointestinal epithelial cell), invasion (i.e., the ability of the organism to enter the cell and thereby bring about its destruction), toxin production (many different toxins are produced), and stimulation of inflammatory responses.[105] It is likely that other mechanisms remain to be described.

Adherence seems particularly significant for *E. coli* and has recently been described in strains of these bacteria associated with chronic diarrhea syndromes of infancy.[75] One of the modes of action of breast milk and locally produced secretory immunoglobulins may be to prevent attachment of bacteria to the intestinal epithelial cells. At least three accessory virulence structures have been identified on the surface of human isolates of enterotoxic *E. coli.*[110] The complex interaction of these components, fimbriae (pili), colonization factor antigens, and the gastrointestinal surface involves chemotaxis, penetration of mucus, adhesion to mucus and cell receptors, and bacterial multiplication. Insight into host defenses includes descriptions of natural inhibition, secretory IgA, competition for attachment sites and nutrients, and alterations in epithelial cell receptors associated with rapid cell turnover. Unravelling these mysteries may provide the basis for future preventive measures and treatments.

Invasive organisms include Salmonella and Shigella, although in the strictest sense, viruses, *Entamoeba histolytica,* and *Giardia lamblia* should be considered invasive as well. That is because these organisms have in common the ability to cause considerable cell destruction and ulceration of the intestinal mucosa. Cellular invasion cannot always be correlated with invasion of the bacteria beyond the gastrointestinal tract. Hence, bacteremia is frequently seen with Salmonella but is uncommon with Shigella infections, despite the fact that both organisms have the capacity to invade cells. There is no satisfactory explanation for this difference, although it may relate to the ability of some strains of Salmonella to resist phagocytosis and/or intracellular killing.

Enterotoxins are important in the pathogenesis of diarrhea due to *E. coli, Staphylococcus aureus, Clostridium perfringens, Vibrio cholerae,* and possibily even *Pseudomonas aeruginosa, Aeromonas hydrophila,* and *Campylobacter.*[326] These toxins can act in several ways.[63] The actions of cholera and *E. coli* toxins are similar, with their net effect being a hypersecretion of fluid and electrolytes into the lumen of the bowel. Despite this similarity, the stool content of sodium is more concentrated with cholera than it is with enterotoxigenic *E. coli.*[260] The most active enterotoxins (those elaborated by *Vibrio cholerae, E. coli,* and *Staphylococcous aureus*) are heat-labile. The functions of heat-stable enterotoxins (*E. coli, Yersinia enterocolitica*) are not well understood.[286] It is also interesting that enterotoxigenic *E. coli* plays only a minor role in the pathogenesis of diarrhea in North America, yet is extremely important in the pathogenesis of diarrhea in developing countries. This may be one of the reasons why traveler's diarrhea (commonly caused by enterotoxigenic *E. coli*) is such a severe illness in visitors from developed countries. Another enigma concerns the role of *C. difficile* toxins[101] in the pathogenesis of pediatric gastroenteritis. Although these substances are either enterotoxic or cytotoxic, or both, by laboratory analysis, they are often found in the stools of asymptomatic subjects, particularly in newborns and infants.[236]

The pathogenesis and etiology of diarrhea syndromes are dynamic features. This is related to community spread of these organisms, the effects of travel, the effects of antibiotic therapy in humans and in animal feeds, and the fact that many of the pathogenic mechanisms are under plasmid control.[105] For example, the control of adherence (colonization factor antigens) and enterotoxins is related to genes contained in plasmids that can be transferred between diverse bacteria. Thus classic bacterial enteropathogens may develop new clinical features (indicative of the acquisition of a new mechanism of pathogenesis), or organisms that are not usually enteropathogenic are associated with outbreaks of diarrhea.

Etiology

As in respiratory infections, the most common causes of gastroenteritis are viruses.[336] Another parallel also exists—that is the fact that as many as 45% of cases of gastroenteritis have no defined etiology. The common causes of diarrhea are outlined in Table 6–1. This list is remarkably consistent around the world, with some exceptions. Parasitic causes of diarrhea and cholera are more common in tropical climates, where amebiasis and hookworm infestations abound. Shigella is also more frequently seen in warmer climates whereas Salmonella, Campylobacter, and Yersinia are more characteristic of temperate and colder climates.

Worldwide, cholera and rotavirus are the commonest causes of gastroenteritis in all populations.[38] Much information about Norwalk agent, a small 27-nm parvovirus-like particle, and its subtypes, is derived from North American studies, and its global impact has not been well examined.[204] Similarly, new information about noncultivatable adenoviruses has reawakened earlier speculation that these agents play an important role in the pathogenesis of gastroenteritis.[415] Older studies, employing classic tissue culture techniques, suggested that the frequencies of adenovirus isolation in children with diarrhea and well children were similar, but recent surveys, using electron microscopy,[46] dispute these findings, based on the frequency of noncultivatable adenoviruses in the stools of the symptomatic patients.[313] Undoubtedly, ECHO and coxsackie viruses can also cause outbreaks of gastroenteritis, although considerable numbers of patients acquire and transiently excrete these agents without symptoms.[40] These may be immune subjects, and the situation may be somewhat analogous to other carrier states, such as described with *Haemophilus influenzae, Neisseria meningitidis*, and even rotavirus.[72]

Newer candidates as causes for diarrhea include *Aeromonas hydrophila,*[58] *Aeromonas sobria,*[66] *Bacillus cereus,*[165] *Plesiomonas shigelloides,*[328] *Cryptosporidium,*[179] and newer, incompletely characterized viral agents (e.g., calicivirus,[88] Snow Mountain agent,[100] coronavirus, and minirotavirus[366]). Some of these viruses, such as calicivirus, may be responsible for clinical outbreaks previously characterized as winter vomiting disease.[89] The roles

TABLE 6–1. Common Causes of Acute Infectious Diarrhea

- Viral
  - Rotavirus
  - Norwalk virus (approximately 27-nm virus)
  - Other viruses
    - Adenovirus
      - Cultivatable in tissue
      - Noncultivatable
    - Enteroviruses (ECHO, coxsackie)
    - Astrovirus
    - Calicivirus
    - Coronavirus
    - Minirotavirus
- Bacteria
  - Salmonella
  - Shigella
  - *Vibrio cholerae*
  - *Vibrio parahaemolyticus*
  - *Campylobacter fetus* ss. *jejuni*
  - *Yersinia enterocolitica*
  - *Escherichia coli*
  - Other bacteria: Aeromonas sp.
- Parasites/Protozoa
  - Giardia
  - *Entamoeba histolytica*
  - *Balantidium coli*
  - Schistosoma
  - Trichinella
- Other parasites that can cause diarrhea
  - *Ascaris lumbricoides*
  - Hookworm (*Ancylostoma duodenale,* and *Necator americanus*)
  - *Trichuris trichiura* (whipworm)
  - Coccidia (*Isospora belli,* and Cryptosporidium *sp.*)[256]

of yeasts, Pseudomonas, and other stool flora, present in high concentrations in the gastrointestinal tract, remain controversial. Even *Streptococcus pyogenes* has been associated with dysentery.[307]

Although *Clostridium difficile* is clearly identified as a cause of pseudomembranous colitis,[394] even in infants,[4] its role in the pathogenesis of antibiotic-associated colitis,[116] necrotizing enterocolitis, chronic diarrhea, and other gastroenteritis syndromes in children is unclear.[402] Part of the confusion derives from the frequent cultivation of this organism and/or detection of its toxin in the stools of normal newborns, infants,[82] and children.[382] Moreover, pseudomembranous colitis can clearly occur in the absence of *C. difficile.*[295]

Gastroenteritis can be grouped according to several different criteria. Table 6–2 describes the etiologies encountered in outbreaks of common source. Some cases are due predominantly to preformed toxins, as seen with staphylococcal infections. Others are associated with ingestion of large numbers of bacteria that have multiplied in the food product; this is seen with *Clostridium perfringens,*[355] *Bacillus cereus,*[165] Salmonella, and *E. coli.*[381] *Vibrio parahaemolyticus, V. fluvialis,*[377] and *V. vulnificus*[177] should be kept in mind when travelers or others report ingestion of raw shellfish, and Edwardsiella in association with ornamental fish.[387] Occasionally, the cause is not directly infectious, but secondary to the capacity of certain bacteria (e.g., Morganella) to convert histidine in tuna or other fish (called scombroid fish poisoning). The released histamine-like substance can cause afebrile gastroenteritis.[14]

Ascaris lumbricoides is one of the most prevalent parasites worldwide, and children have high rates of infection. Most are asymptomatic, however, and acute and chronic diarrhea are rare features of ascariasis, although vomiting may accompany intestinal obstruction.[398] Sometimes adult worms are seen in the vomitus; enough, in some cases, to look like spaghetti. Biliary obstruction, malnutrition, and hypersensitivity pneumonitis may also result. The diagnosis is usually made by visualization of ascaris eggs in the stool. Treatment with piperazine is highly effective (Chapter 2).

Occasionally larvae (e.g., myiasis) and worms, such as *Dipylidium caninum* (dog tapeworms), are seen in the stools of asymptomatic infants or children.[237] Irritability, restlessness, anorexia, poor weight gain, pruritus, and abdominal pain may occur.[154] A single dose of niclosamide (see Chapter 2) is curative.

The diagnosis and management of other intestinal nematodes (hookworms, tapeworms, pinworms, Strongyloides, Trichuris, and Capillaria) have been recently summarized[77] and are also considered in Chapter 2. Eosinophilia in association with peptic ulcer symptoms suggests the possibility of strongyloidiasis.[196] Some of these children may have asthma as well.[18]

As detailed above, epidemiologic history can be important in suggesting the etiology. Thus, information about travel, attendance at day-care centers, common food or water exposure, diarrhea in other family and community members, and the season of the year is useful.[147]

Chronic diarrhea (variably defined as lasting more than 2 weeks, or more than a month) has many causes, most of which are noninfectious.[126] Giardia is probably the most common direct infectious cause of chronic diarrhea but still is less frequently responsible than postinfectious intolerances due to mucosal damage and acquired disaccharidase deficiency. Occasionally, Campylobacter, *Mycobacterium tuberculosis,*[140,303] Salmonella, adherent enteropathogenic *E. coli,*[75] *C. difficile,*[224] Yersiniae, or amoebae may be responsible. The role of some parasites, such as *Dientamoeba fragilis,*

TABLE 6–2. Food- or Waterborne Diarrhea

Agent	*Incubation Period*	*Other Clinical Manifestations*	*Diagnosis*
Bacillus cereus	1–24 h	Vomiting Abdominal cramps	Culture from water/food ± stool
Campylobacter fetus ss. *jejuni*	2–5 days	Vomiting, fever Abdominal cramps	Culture from water/food ± stool
Clostridium perfringens	9–15 h	Abdominal cramps	Culture from food ± stool
Entamoeba histolytica	2–4 weeks	Dysentery	Cysts in water or trophozoites or cysts in stools
Escherichia coli	6–36 h	Vomiting	Culture from water/food ± stool
Giardia lamblia	1–4 weeks	Chronic diarrhea Weight loss	Demonstration of trophozoites or cysts in water, stool, or duodenal aspirates
Norwalk virus	16–72 h	Vomiting Abdominal cramps	Electron microscopic (EM) demonstration of virus in stool. Seroconversion
Rotavirus	24–72 h	Vomiting, fever Abdominal cramps	EM or ELISA demonstration of virus in stool. Seroconversion
Salmonella	6–48 h	Abdominal cramps, fever	Culture from water/food ± stool
Shigella	12–50 h	Abdominal cramps, fever Dysentery, seizures	Culture from water/food ± stool
Staphylococcus aureus	0.5–8 h	Vomiting Hypotension	Culture from water/food ± stool ± vomitus Enterotoxin in food
Vibrio cholerae	1–5 days	Vomiting	Culture from food ± stool ± vomitus. Seroconversion
Vibrio parahaemolyticus	4–30 h	Abdominal pain Pseudoappendicitis	Culture from food ± stool
Yersinia enterocolitica	3–7 days	Abdominal pain, fever	Culture from water/food ± stool

in the pathogenesis of diarrhea is unclear. A therapeutic trial of diiodohydroxyquin 40 mg/kg/day for 20 days has been suggested for selected cases, but only after exclusion of more conventional causes of diarrhea.[191] In the strictest sense, contaminated small bowel syndromes (colonic flora in the small bowel) secondary to congenital or acquired obstructions, malrotations, etc. (often seen after gastrointestinal surgery) could be considered infectious. Gastrointestinal coccidiosis (Cryptosporidium or Isospora) suggests the presence of cellular immunodeficiency conditions, including AIDS, in which these infections may also be associated with salmonellosis and candidiasis.[12] Causes of noninfectious diarrhea are listed in Table 6–3.

Clinical Manifestations

The predominant signs of gastrointestinal infection are vomiting and diarrhea. Vomiting is more frequently seen with rotavirus and Norwalk agent infections and less common with most bacterial and parasitic causes of diarrhea. Vomiting usually precedes diarrhea and is more short-lived, rarely lasting more than 1–2 days. It is useful to describe diarrhea as either "cholera-like" (watery) or "dysentery-like" (mucus and/or blood). The former is more characteristic of toxigenic causes of diarrhea (e.g., cholera, enterotoxigenic *E. coli*), and the latter more frequently seen with invasive infection (e.g., amebiasis, shigellosis, and Campylobacter gastroenteritis). Recently, a dysentery syndrome with severe cramping abdominal pain and grossly bloody stools has been described due to *E. coli*.[318] Salmonella, *Vibrio parahemolyticus,* and *Yersinia enterocolitica* infections often result in production of greenish stool (sometimes described as "pea-soup-like") without the above features. In this way, description of the stools allows more specific inquiry into cause and can guide the clinician in selecting diagnostic procedures and management.

Other signs of gastroenteritis include fever, which commonly precedes Shigella, Campylobacter, and Yersinia infections. It is also present in over 90% of infants with rotavirus diarrhea.[336] Conversely, it is uncommon in school-age children with Norwalk agent gastroenteritis and may also be absent in parasitic gastroenteritis. Some of the characteristics of gastroenteritis associated with food or water-borne outbreaks of diarrhea are listed in Table 6–2. Perianal pruritus and worms in the stool may be the only signs of the presence of pinworms (*Enterobius vermicularis*) in the gastrointestinal tract, but, occasionally, appendicitis, and even salpingitis and peritonitis may occur.[292]

Selected features of diarrhea syndromes are summarized in Table 6–4. Other manifestations may reflect extragastrointestinal involvement. Hence, bacteremia is common and rose spots can occasionally be seen with Salmonella (and rarely, Shigella),[139] visceromegaly with leishmaniasis, anemia with hookworm infection, and severe abdominal pain with

TABLE 6-3. Noninfectious Causes of Diarrhea

- Drugs and chemicals including antibiotics
- Postinfectious
  - Secondary disaccharidase deficiency, intolerances, bile salt malabsorption
- Inflammatory bowel disease
  - Ulcerative colitis
  - Regional enteritis
- Psychogenic
- Neoplastic
  - Carcinoid
  - Neuroblastoma
  - Zollinger-Ellison
  - Ganglioneuroma
- Anatomic: congenital
  - Malrotation
  - Hirschsprung
- Postsurgical
  - Blind loop syndrome
  - Short bowel syndrome
- Malabsorption
  - Sprue syndromes, celiac disease
- Pancreatic insufficiency
  - Cystic fibrosis
  - Shwachman syndrome
- Carbohydrate intolerance
  - Lactose
  - Sucrose-isomaltose
  - Monosaccharide
- Protein intolerance
  - Allergy
  - Enterokinase deficiency
  - Trypsinogen deficiency
  - Amino-acidopathies
- Allergic
  - Cow's milk protein
- Endocrine-metabolic
  - e.g., Hyperthyroid states, hypoadrenalism
- Antibody deficiency syndromes
- Acrodermatitis enteropathica
- Benign lymphatic hyperplasia of the rectum
- Diet
  - Candy containing hexitols
- Idiopathic acute and persistent diarrheas

TABLE 6–4. Characteristics of Selected Causes of Diarrhea

	Rotavirus	*Norwalk*	*Salmonella*	*Shigella*	*Campylobacter*	*E. coli* (*toxigenic*)	*E. coli* (*invasive*)	*Yersinia*	*Cholera*
Peak age	6–24 months	School age	All ages	All ages	1–5 Years	All ages	All ages	20–26 Months	Endemic-children > 1 year, epidemic-all ages
Season	Winter (year-round in tropics)	Winter	Year-round	Warm seasons	Summer (year-round in tropics)	Summer (year-round in tropics)	Uncertain	Summer/fall	Summer
Vomiting	Common	Common	Uncommon	Rare	Less common (1/3)	Common	Common	Less common (1/3)	Uncommon
Abdominal pain	Rare	Common	Common	Common	Common	Common	Common	Common	Uncommon
Fever	Common (90%)	Low-grade	Common	Common	Less common (2/3)	Variable	Common	Less common (2/3)	Common
Respiratory symptoms	Variable (50%)	Rare	No	No	Rare	No	No	Rare	No
Dehydration	Common	Rare	Rare	Rare	Rare	Common	Uncommon	Rare	Common
Blood in stool	Rare	Rare	Rare	Common	Common	Rare	Common	Less common (1/4)	No
Average duration of diarrhea	5 Days	1–3 Days	7 Days	2–4 Days	6 Days	3–5 Days (14–21 in some infants)	3–5 Days	14 Days	4–5 Days
Average duration of stool excretion of pathogen	5 Days	3 Days	2 Weeks, 12–14 weeks in infants < 3 months	1–2 Weeks	25 Days	1 Week	1 Week	42 Days	1 Week
Seizures	No	No	No	Yes	Occasionally	No	No	No	Yes

Yersinia[241] and Campylobacter infection,[102] both presumably due to mesenteric lympadenitis. In fact, the abdominal pain can be so severe in these infections that "pseudoappendicitis" syndromes are described, leading to exploratory laparotomy and appendectomy in many patients.[39] Other clinical manifestations, such as meningismus and seizures with shigellosis, are frequently observed, although their pathogenesis is not completely understood.[24] The diagnostic possibility of gastroenteritis may be forgotten when the earliest clinical manifestations are fever or seizures. We see this situation often in nosocomial gastroenteritis and shigellosis, respectively. Long-term carrier states are common in adults (not in children) with Salmonella but rare with Shigella[220] and other enteric pathogens (except *Entamoeba histolytica,* where asymptomatic patients who excrete cysts are encountered). Excretion of Salmonella in the stools of recovering young infants may be noted for a 2–3-month period.[193]

Diagnosis

As outlined in Table 6–2, outbreaks of common source, the duration of the incubation period, and the clinical manifestations may suggest the etiologic diagnosis. This is also clear (but too frequently forgotten) in a situation where one family member has a Shigella infection and another develops gastroenteritis. What is less easy to diagnose is the sporadic case of gastroenteritis in the community, or the traveler who returns from a trip to a tropical climate where several enteropathogens predominate.[111]

Before discussing specific diagnostic tests, it seems worthwhile to ask when to investigate the etiology of diarrhea. Since the vast majority of gastrointestinal infections are self-limited and benign, and due to viruses and other agents not responsive to specific therapy, most cases require little laboratory investigation in the first few days of illness. Exceptions include the newborn, the immunologically abnormal host, the severely ill individual, and the patient with a prolonged or atypical course of illness. For example, the child with sickle-cell anemia is particularly prone to invasion and extragastrointestinal infection by Salmonella.[122] Yersinia, Campylobacter, Shigella,[118] and Salmonella may also be problems for patients with leukemia and those receiving immunosuppressive drugs. If the patient does not have fever, or there is no clear history of travel or contact with infection, or the cause of illness seems atypical, noninfectious causes of diarrhea should also be considered (Table 6–3).

Laboratory procedures useful in the diagnosis of the specific cause of diarrhea include microbiologic techniques for culturing enteroviruses and bacteria, and examination of stool for ova and parasites (Table 6–5). Familiarity with the growth requirements and colonial morphology of the enteric bacilli is critical (Fig. 6–1). The gram or 1% aqueous basic fuchsin-stained stool smear may be useful if large quantities of vibrio-shaped organisms are seen[346] (Fig. 6–2). This can point to a diagnosis of cam-

TABLE 6–5. Laboratory Diagnosis of Infectious Diarrhea

Rapid methods	
Rotavirus antigen-ELISA method	
Rotavirus	Electron microscopy
Norwalk virus	
Adenovirus	
Other viruses	
Campylobacter/Vibrio: Gram stain	
C. difficile toxins-ELISA or CIE	
Parasites: smear	
Selective/enrichment media helpful	
C. difficile: Cycloserine, cefoxitin agar	
Yersinia enterocolitica: Cold enrichment in phosphate-buffered saline	
Campylobacter: Skirrow's medium, incubation at 42°C	
Salmonella: Selinite broth	
Shigella: Hektoen enteric agar	
Vibrio: Thiosulfate-citrate-bile salts	

pylobacteriosis, *Vibrio cholerae,* or *Vibrio parahemolyticus.* Methylene blue stain of the stool can also be useful, since polymorphonuclear leukocytes are rarely seen with viral pathogens, amebiasis, or toxigenic bacteria.[298] An exception to this is pseudomembranous colitis, thought to be due to toxigenic *C. difficile,* yet also associated wtih colonic ulceration, pseudomembrane formation, and polymorphonuclear leukocytes in tissue and stool. Stool leukocytes in normal children with diarrhea are seen with Shigella, early Salmonella, Yersinia,[229] Campylobacter[228] infections, and with amebiasis.

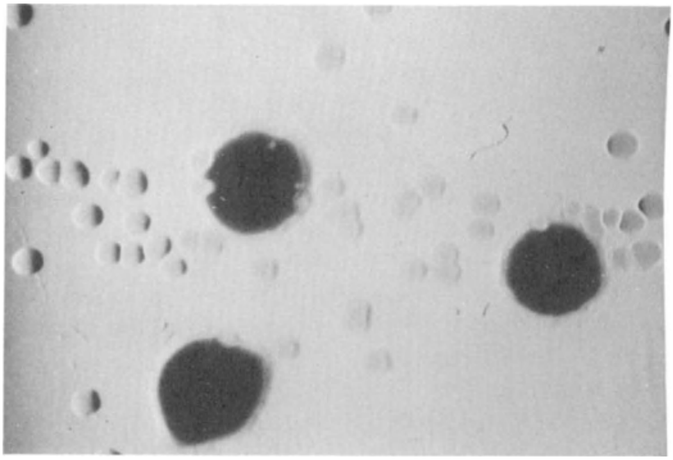

Figure 6–1. Small lactose-negative colonies of *Yersinia enterocolitica* adjacent to large lactose-positive *E. coli.*

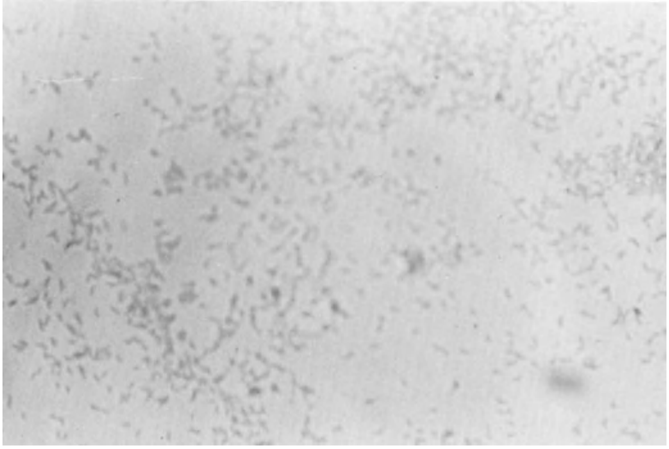

Figure 6–2. Gram stain of *Campylobacter fetus*.

Enzyme-linked immunosorbent assay (ELISA) is used for the rapid detection of rotavirus antigen in stool.[368] Electron microscopy can also be used and is more accurate in newborns than the rotazyme.[205] Other viral causes of diarrhea, such as Norwalk agent, noncultivatable adenoviruses, calicivirus, etc., can be directly visualized by electron microscopy of stool, or diagnosed indirectly by means of serology.[147] Serologic diagnosis is possible for viral and bacterial causes, including campylobacter,[183] but is rarely used in acute cases. It is most useful for epidemiologic study, in the diagnosis of chronic diarrhea, or for cases with atypical courses or extragastrointestinal manifestations. Chronic diarrhea may be due to Giardia, also diagnosed by visualization of the cysts or trophozoites in the stool or the trophozoites in duodenal aspirates.[255] The latter can be obtained by direct suction of duodenal contents, duodenal biopsy, or by a string test. In this method, string is enclosed in a capsule, which is swallowed by the patient and then pulled back after 4 h. After this time, it has usually become soaked with duodenal mucus and can be studied for the presence of parasites.[322] Countercurrent immunoelectrophoresis can also be used to detect Giardia antigens in feces.[86] Amebic trophozoites with ingested red blood cells are best seen in wet mount preparations of ulcer scrapings or in rectal mucus. Serology may also be useful in the diagnosis of amebiasis.[97] Associations of Yersinia gastroenteritis with arthritis and thyroid disease (usually encountered in the convalescent period) can also be defined serologically.[242]

Toxin assay is most useful for the diagnosis of *C. difficile*-associated diarrhea. Counterimmunoelectrophoresis or ELISA can be used for this purpose, but both depend on the specificity of the antibody, a nonstandardized testing material at this time.[417] Selective culture media are required for growth of *C. difficile* from stool.[49]

Treatment

The treatment of gastroenteritis can be considered in three different ways: supportive, symptomatic, and antimicrobial. The supportive therapy of gastroenteritis refers to the use of fluids, electrolytes, and nutritional intake appropriate to the age of the patient and the manifestations of the infection. Patients with toxigenic, watery diarrhea need to be watched closely for dehydration, although this may also be a manifestation of shigellosis, even in the absence of profuse diarrhea. This is due to a "third space effect" referable to the accumulation of large volumes of fluid and electrolytes within the lumen of the bowel before the advent of fulminant diarrhea. This is particularly a problem in young infants. In many situations, rehydration can be accomplished orally by use of hypotonic (Na of 40–50 mEq/liter and approximately 5–10% carbohydrate) electrolyte solutions.[123] A rice-based electrolyte solution has been particularly effective.[290] Rehydration can be done more precisely in hospital with monitoring of serum electrolyte concentrations. Patients with hypertonic dehydration and those with hypotension secondary to intravascular volume depletion require hospitalization, intravenous fluids, and careful monitoring of intravascular volume and electrolyte content. The vast majority of patients, however, can be managed with oral rehydration and their course is usually self-limited. Most practitioners use a brief period of "gastrointestinal rest" in school-age patients and a clear fluid program for these patients for the remainder of a 24–48-h period. This is more difficult to do in young infants, where dehydration can rapidly occur; therefore, these patients are usually managed with more aggressive fluid replacement from the onset of their symptoms. Feeding stimulates the gastrointestinal tract in three ways, namely, stimulation of the gastrocolic reflex, responses to bulk within the gastrointestinal lumen, and osmotic effects of intralumenal contents. Thus, it seems logical to feed infrequently and with small volumes, and to avoid solids or excessive amounts of sucrose. It should be kept in mind that a considerable number of infants rapidly develop disaccharidase deficiencies, which lead to lactose and sugar intolerances and malabsorption.

Symptomatic therapy of diarrhea is a controversial issue. Table 6–6 outlines some of the therapies that have been tried in order to control the discomfort associated with gastroenteritis. These are rarely useful in infants and children and may, in fact, be harmful. The simplest approach is to avoid solids and allow the gastrointestinal tract to expel the infectious agents and their products as quickly as possible. After all, diarrhea and vomiting are host defense mechanisms, as well as signs of infection.

Specific antimicrobial therapy[120] is rarely indicated in most diarrhea syndromes with some exceptions (Table 6–7). The course of Shigella infection can be effectively shortened by early antimicrobial therapy, but the advantages of therapy become fewer as spontaneous improvement

TABLE 6–6. Pitfalls of Symptomatic Treatment for Pediatric Patients with Infectious Diarrhea

Agent	*Effect*	*Reference*
Lactobacillus	No prophylactic effect	76
	No therapeutic effect	291
Loperamide	Drowsiness/coma	235
Kaolin-pectin	No therapeutic effect	304
Diphenoxylate with atropine/codeine	Increased toxicity of bacterial diarrhea	274
Iodoxychloroquine	Optic neuropathy	127
Diiodohydroxyquin		275
Oral rehydration fluids	Chronic diarrhea	143

occurs.[135] Bacteriologic excretion is also reduced and this may prevent spread to susceptible contacts. Campylobacter[10] infections and cholera can also be treated with antibiotics, but unlike Shigella infections, the clinical course is not affected.[319] The major effect is on bacterial excretion. When Salmonella[192] and Yersinia[284] infections are restricted to the gastrointestinal tract, antibiotic therapy affects neither the course of the illness nor bacterial excretion. The role of antibiotic therapy in the treatment of *E. coli* infections, whether due to enterotoxigenic, adherent, or invasive strains, is unclear, as is the treatment of *C. difficile*-associated diarrhea.[360] Whenever antibiotics are used, the risks of the drug, selection of resistant strains, and the expense must be borne in mind. Trimethoprim/sulfamethoxazole (or amoxicillin if the bacteria are sensitive) can be effectively used in the treatment of severe *E. coli* diarrhea not due to enterotoxin-producing strains.[383] Since many antibiotics can also cause diarrhea, the indications for their use must be clear.[403] Remember also that indiscriminate use of antibiotics to prevent diarrhea in travelers and family contacts has led to the widespread development of plasmid-mediated resistance in several enteropathogens.[111]

Intestinal giardiasis can be treated with either quinacrine (7 mg/kg/day divided t.i.d., maximum 300 mg/day) × 5 days or furazolidine in the same dose × 10 days. The latter drug is often better tolerated in children under 5 years of age.[85] If the patient is symptomatic, *Entamoeba histolytica* intestinal infections (amebiasis) can be treated with either metronidazole (50 mg/kg/day divided q 8 h; maximum 2 g/day) or chloroquine phosphate.[201] A 10-day course is usual. Asymptomatic patients who excrete amebic cysts can be given diiodohydroxyquin 30–40 mg/kg/day × 20 days (divided q 8 h, maximum 2 mg/day) or diloxamide furoate 20 mg/kg/day (divided t.i.d.) × 10 days.

The diagnosis and treatment of other intestinal protozoan infections including those caused by *Dietamoeba fragilis, Balantidium coli,* and *Isospora belli* have recently been reviewed.[410]

Complications

Infectious gastroenteritis is usually uncomplicated. Any parent can attest to the unhappiness it creates in the home, and we are all aware of the distressing effect these infections have on us. In the majority of cases, however, the illness rarely lasts longer than 2 days in its peak intensity and more than 5 in total. Nonetheless, young infants are particularly prone to secondary effects of infectious gastroenteritis, including dehydration, lactose intolerance, and chronic diarrhea.[19] Disaccharidase deficiencies may be due to the direct effects of the bacteria on the epithelial cells containing these enzymes. Several weeks to months may be required for reepithelialization and complete recovery of disaccharidase enzyme activity. Steatorrhea may also be encountered in young infants with viral gastroenteritis.[226] These effects are particularly prevalent in infants acquiring gastroenteritis in the first 3 months of life, and may last up to 1 month. These factors should be considered in planning dietary management of young infants during convalescence.

Bacterial and yeast overgrowth may also be seen as sequelae to infectious gastroenteritis or due to antibiotic therapy. In such instances, *Pseudomonas aeruginosa*[325] and *Candida albicans*[185] have been implicated in the pathogenesis of symptomatic exacerbations, although their causative roles are controversial. Discontinuation of the offending antibiotic is usually the treatment of choice.

TABLE 6–7. Antimicrobial Treatment of Acute Infectious Diarrhea

Shigella	
Ampicillin 100 mg/kg/day	× 7 days
or	
Trimethoprim/sulfamethoxazole 10 (TMP)/50 (SMZ) mg/kg/day	
or	
Moxalactam 100 mg/kg/day	
or	
Chloramphenicol 75 mg/kg/day	
Campylobacter	
Oral erythromycin 40 mg/kg/day × 5 days	
E. coli	
Oral colistin 15 mg/kg/day × 3 days	
C. difficile	
Oral vancomycin 50 mg/kg/day × 10 days	
Oral metronidazole 30 mg/kg/day × 10 days	
Cholera	
Oral trimethoprim/sulfamethoxazole 10 (TMP)/50 (SMZ) mg/kg/day × 3 days	
Oral tetracycline (for children > 8 years) 30 mg/kg/day × 3 days	

Chronic diarrhea is always a possibility after an acute episode of infectious gastroenteritis. This complication can be due to enzyme deficiencies, malabsorption, bacterial overgrowth in the upper small bowel, or the presence of specific adherent *E. coli* organisms.[126]

The gravest complications of gastrointestinal infections are extragastrointestinal involvement. Hence, Salmonella bacteremia and focal Salmonella infections outside the gastrointestinal tract may be life-threatening. This is also true with other bacterial and parasitic causes of gastroenteritis (e.g., amebic liver abscess after gastrointestinal amebiasis). Although invasion beyond the gastrointestinal tract is rare with viral causes of gastroenteritis, dehydration, electrolyte abnormalities, and their consequences may be grave complications. Moreover, these agents may complicate the course of patients with serious underlying conditions. For example, gastroenteritis associated with adenovirus, rotavirus, coxsackievirus, and *C. difficile* contributes to excessive mortality in bone marrow transplant recipients.[414]

Bacteria associated with gastroenteritis are most likely to invade beyond the gastrointestinal tract in hosts predisposed by young or old age, chronic disease, underlying malignancies, hemoglobinopathies, and immunodeficiency syndromes, as well as immunosuppressive states induced by drugs or intercurrent illnesses.

Prevention

The critical difference between the frequency and severity of diarrheas in developed countries and those in rural underdeveloped areas relates to the availability of public health facilities and level of hygienic practices. Proper sewage disposal, clean drinking water, and available facilities for handwashing, preparation and storage of food, and adequate nutrition are of major importance.

Attempts to curtail the expression of diarrhea syndromes by use of vaccination have been largely unsuccessful.[104] This is due to the inadequacy of currently available vaccines and the extreme heterogeneity among causative agents. Of the currently available products, cholera vaccine is most frequently used. This product is a formalin-killed whole bacterial cell vaccine and confers effective immunity in approximately 50–70% of cases. Unfortunately, this immunity lasts for only 2–4 months and requires frequent boosting. In many situations, the vaccine side effects (local pain, fever) outweigh the benefits. This is particularly true for American travelers, whose risk of acquiring cholera seems very small.[363] Other vaccines are in a more experimental stage of development and their use will probably be restricted to travelers, curtailment of specific outbreaks, or particularly high-risk populations.

In institutional outbreaks, antibiotic therapy may be used to control the spread of shigellosis. One must be very careful to identify the causative organism and its susceptibilities, lest an inappropriate antibiotic is used. In selected circumstances, antibiotics may also be used to prevent spread of Campylobacter, Shigella, and *Vibrio cholerae* within family units. It should be remembered that the later in the illness these antibiotics are used, the less likely they are to influence the clinical course and the more prone to favor the selection of resistant strains. When used in community outbreaks, this approach has been associated with development of resistance among Salmonella, Shigella, and *E. coli* strains.

Nosocomial gastroenteritis is an important problem and often reflects the simultaneous spread of several pathogens, including rotavirus, Salmonella and, occasionally, *E. coli.*[366] Principles of prevention are similar to those discussed for day-care centers and institutions. Handwashing is the most important preventive measure, followed by adequate space and staff, and proper disposal of diapers and excreta.

Travelers can best avoid diarrhea by careful attention to eating and drinking habits.[111] Avoiding preformed toxins in contaminated food and water is critical. Although antimicrobials have been used, their toxicities and the variable susceptibilities of infectious agents have led to failure in many cases. Doxycycline has been used to prevent traveler's diarrhea with some effectiveness, but recently, doxycycline-resistant enterotoxigenic *E. coli* have become a problem in several geographic areas.[338] Trimethoprim/sulfamethoxazole may also be effective, but this has not been evaluated in young children.[106] Prophylactic use of lactobacilli is ineffective,[76] as is the use of diphenoxylate with atropine and other antimotility drugs. These are particularly dangerous if Shigella species, amoeba, or enterotoxigenic bacteria are present. Subsalicylate bismuth has been used to protect against diarrhea. The large dosages recommended may fill a suitcase, and can also lead to excessive salicylate absorption in young children.[296] Any of these approaches for traveler's diarrhea is intended only as prophylaxis. Onset of diarrhea despite their use should stimulate an aggressive search for the etiologic diagnosis and specific management.

Breast-feeding remains an essential defense for the prevention of infectious gastroenteritis in developing countries.[404] The immune substances provided in breast milk create an effective first line of defense against ingested enteric pathogens and can reduce the frequency and severity of diarrhea in many infants.[270] Human milk even has the capacity to kill Giardia, amoeba, and Trichomonas.[134] Even though gastrointestinal colonization (and, therefore, possible communicability) of *V. cholerae* is not reduced by the presence of breast milk antibodies against cholera toxin and lipopolysaccharide (endotoxin), disease is reduced.[137] Although this approach is strongly recommended for developing populations, the primary roles of adequate nutrition and personal and community hygiene also deserve emphasis.

Rotavirus Infection

Epidemiology

Rotavirus infections deserve extra comment because they are probably the most common cause of acute infectious diarrhea in young infants and children in industrialized countries. In one recent survey in Trinidad, rotavirus was associated with 23% of cases of diarrhea, whereas Salmonella, the next most common recognized cause, was present in only 7%.[168] Our knowledge of human rotavirus infections is relatively young with regard to its clinical expression, characteristics of the virus, and prospects for prevention.[368]

Diagnosis

The diagnosis of rotavirus infections has been facilitated by the development of an immunoassay for the detection of rotavirus antigen in stool. The sensitivity of this test is comparable to that of electron microscopy, but both methods require the presence of approximately 10^7 virus particles/ml of stool.[323]

Clinical Manifestations

The entire spectrum of rotavirus infection is yet to be described. Gastrointestinal disease has been noted in individuals of all ages ranging from newborns to adults. Nosocomial outbreaks have been described in nurseries, maternity units, and institutions for the aged. Although upper respiratory infection has been noted in as many as half of the patients with rotavirus infection, attempts to detect rotavirus antigen in respiratory secretions have rarely been successful.[339] Most rotavirus infections manifest as self-limited gastroenteritis, although chronic diarrhea has been described in a child with X-linked immunodeficiency.[341]

Most young infants in the first 2 years of life have some lactose intolerance after rotavirus gastroenteritis. Because this may last up to 2 or 3 weeks, it is useful to restrict lactose-containing foods for this period of time, especially in the young patients with more severe clinical illness.[170]

Rare complications associated with rotavirus gastroenteritis have been described, including intussusception,[203] Reye syndrome and encephalitis,[333] sudden infant death syndrome,[416] and fatal disease in young infants with severe dehydration.[62]

Treatment/Prevention

The disease is extremely frequent in winter months in temperate climates and nosocomial spread is unusually high.[321] As usual with enteric infections, handwashing is critical.[334] Our knowledge of the pathogenesis of this disease is improving and preliminary experience with an oral vaccine is encouraging.[393] One recent study, however, may also provide a useful approach.[23] These investigators administered 4 ml of pooled human serum immunoglobulin orally four times a day to premature babies in the first week of life during an outbreak of rotavirus gastroenteritis in a newborn nursery. They were able to prevent diarrhea in 13 of 14 infants treated with gammaglobulin, while only 5 of 11 infants treated with placebo remained asymptomatic. If confirmed, this approach may offer a means of reducing the morbidity of rotavirus in closed populations and in protecting certain high-risk individuals.

Salmonellosis

Pathogenesis

Salmonella are ubiquitous bacteria that have the capacity to persist within phagocytic cells. The bacteria have several pathogenic capabilities, including invasiveness, resistance to phagocytosis, and resistance to intracellular killing. Host factors that favor invasion include achlorhydria and other underlying gastrointestinal abnormalities, hemoglobinopathies, malignancies, immunosuppression, and the extremes of age. Infants in the first 3 months of life seem at particularly high risk.[271] Malnutrition and debilitation due to a variety of causes are also major determinants of complicated salmonellosis. The size of the inoculum, which may be very great in areas with poor hygiene, may also determine invasiveness and virulence of this organism. In many respects, these infections resemble tuberculosis and brucellosis more closely than disease due to acute pyogenic pathogens. Although most of the time Salmonella infections are limited to the gastrointestinal tract, occasionally these bacteria invade other sites, resulting in chronic and relapsing infections, including typhoid and enteric fevers.

Epidemiology

Patients with liver and biliary tract disease, and infants under the age of 3 months, are particularly prone to excrete Salmonella organisms long after infection. In one series, 27% of these infants were still shedding Salmonella organisms in their stools 8 weeks after acute gastroenteritis.[193] The incidence of extragastrointestinal complications also seems enhanced in infants < 3 years of age.[91]

Marijuana was recently implicated as the vehicle for spread of salmonellosis in 85 people in four states.[380] The bulk of Salmonella infections, however, still emanate from contaminated food, mostly fowl and dairy products. Pets, particularly turtles, frogs, dogs and cats, are frequently implicated as reservoirs as well.[79] Person-to-person spread is significant in outbreaks involving infants in families[407] and day-care centers.[222]

Clinical Manifestations

When Salmonella organisms invade beyond the gastrointestinal tract, the expression of clinical infection is extremely wide (Table 6–8). Abscesses of almost every organ and tissue of the body have been reported, as have acute and persistent bacteremias. Recurrent bacteremias are occasionally seen in patients with concomitant gastrointestinal parasitosis, such as intestinal schistosomiasis. Perhaps the parasites erode the intestinal epithelial defenses and allow Salmonella organisms to periodically enter the vascular system. It is important to remember that predisposed patients (see Epidemiology above) are more likely to have extragastrointestinal manifestations.

Therapy

Although Salmonella gastroenteritis usually should not be treated with antibiotics, several exceptions are noteworthy. These include infants under 3 months of age[271] and the elderly, as well as those predisposed by malnutrition, debilitation, and other underlying conditions. Occasionally, patients with ulcerative colitis are thought to have an exacerbation of their underlying disease, when, in fact, they have an intercurrent infection with an enteric pathogen.[207] In such cases, granulomatous histopathologic changes may be seen with Salmonella infection; however, the possibility of a combined infection should not be forgotten. This is illustrated by the reported coincidence of tuberculous and Salmonella osteomyelitis.[374]

Several characteristics of extragastrointestinal salmonellosis need to be

TABLE 6–8. Extragastrointestinal Complications of Salmonella Infections

Enteric fever/septicemia[91]
Meningitis[91]
Osteomyelitis[2]
Arthritis[281]
Urinary tract infection[29]
Soft tissue abscess[209]
Endophthalmitis[401]
Endocarditis[175]
Pericarditis[374]
Mycotic aneurysm[288]
Erythema nodosum[264]

remembered, if therapy is to be appropriately prescribed. These infections are generally insidious in onset (often extragastrointestinal infections are noted 2–6 months after the episode of gastroenteritis). In addition, the lesions are often localized with minimal systemic signs and symptoms. The degree of destruction of bone and other tissues, however, may be extensive.[281] Antibiotic therapy needs to be prolonged in almost all cases (a minimum of 3 weeks for acute extragastrointestinal infections such as meningitis, and at least 3 months for more chronic extragastrointestinal manifestations, such as osteomyelitis and endocarditis). Often, it is necessary to combine such antibiotic therapy with surgical drainage. In all such cases, careful monitoring of compliance, serum concentrations of antibiotics, and radiographic and other laboratory parameters should be followed extremely closely. Relapses with shorter durations of therapy (and occasionally with long durations of therapy) may be seen several months after completion of apparently adequate regimens.

In choosing antibiotics, one must be aware of the community prevalence of Salmonella susceptibility patterns, often affected by antibiotic use in animals.[276]

Control

Community and personal hygiene, with emphasis on sewage control and clean food and water, remain the major mechanisms for control of Salmonella infections. Handwashing and proper disposal of feces are appropriate for isolation of these patients in hospital and at home. The greatest reservoirs of Salmonella organisms, however, exist in the food chain and in human carriers. Vaccine development research continues, but a useful product is far from a reality at this time.[113]

Campylobacteriosis

Campylobacter infections are becoming more widely recognized worldwide,[278] now that the bacteria's microbiologic characteristics (e.g., the need to incubate the stool culture at 42°C and in a specific gaseous environment) are more familiar.[43]

Epidemiology

Like other enteric bacterial pathogens, Campylobacter species seem widespread in nature. Thus, outbreaks have been described in association with contaminated water,[287] raw milk,[250] processed milk;[182] also implicated have been healthy and ill cats,[44] puppies,[41] hamsters,[130] and ducks.[263] Humans may also serve as reservoirs, as noted in neonatal infections (spread from mother to newborn infant)[9] and in day-care centers.[45]

Clinical Manifestations

The usual expression of Campylobacter infection is gastroenteritis. However, in some populations, such as in India and Bangladesh, asymptomatic infections are common.[136] In newborns, the disease may be mild with diarrhea but no fever and no bacteremia.[9] Abdominal distension is common in infants less than 3 months of age.[269] In others, the disease may simulate a full-blown attack of ulcerative colitis.[69] In one such case, the use of steroids in a 4-year-old with chronic enterocolitis resulted in death before recognition of the presence of campylobacteriosis.[78] Occasionally, as with Shigella gastroenteritis, seizures may accompany diarrhea.[232] Campylobacter appendicitis has also been reported.[68]

Complications

Bacteremia,[317] hemolytic-uremic syndrome, focal abscesses, and erythema nodosum are described (Table 6–9). The duration of fever, diarrhea, and excretion of *C. fetus* in the stool are increased in immunodeficient children.[252] The arthritis described with Campylobacter gastroenteritis may be associated with the acute or convalescent phase of the intestinal infection. Except in rare cases in the acute phase, the joint fluid is usually sterile. This "reactive arthritis" has been, as have other enteric-associated arthritides, associated with a high prevalence of the haplotype HLA-B27. For example, five of seven such patients in Finland had this haplotype, whereas it is present only in 14% of the normal Finnish population.[210] Placentitis with resultant abortion has also been confirmed in a number of cases.[80] It is likely that more extragastrointestinal manifestations of campylobacteriosis will be recognized as microbiologic recognition of this bacteria increases.

TABLE 6–9. Extragastrointestinal Complications of Campylobacter Infections

Arthritis[353]
Bacteremia[146]
Colitis[78]
Meningitis[273]
Hemolytic-uremic syndrome[359]
Erythema nodosum[212]
Guillain-Barré syndrome[81]
Convulsions[56]
Pancreatitis[300]
Vascular infections[244]

Treatment

Treatment of these infections, if they are localized to the gastrointestinal tract, is possible with erythromycin or tetracycline. Bacteriologic shedding is curtailed; however, the clinical course is not usually altered.[285] Rarely, resistant strains are found. Thus, in vitro susceptibility studies should be carried out in complicated cases with persistent infection. More serious invasive campylobacteriosis should be treated with ampicillin, chloramphenicol, aminoglycosides, or imipenem (thienamycin).[6] Other control measures for Campylobacter revolve around the same principles of hygiene and isolation outlined for other enteric bacterial pathogens.

Shigellosis

Diagnosis

Shigellosis is frequent worldwide, but is more prevalent in warmer climates. The persons affected most often are children 1–5 years old.[42] Rapid diagnosis is important because treatment, if initiated early, can decrease bacteriologic excretion and duration of clinical illness. Thus, knowledge of contact with shigellosis (such as in day-care centers or from household members) might facilitate early diagnosis and treatment. The presence of blood or mucus, or both, in the stools, and the presence of neutrophils on microscopic examination of the stool, are also helpful features. The presence of peripheral blood leukocytosis is less consistent, although analysis of the differential white blood cell count might be helpful. In a recent study of this feature of shigellosis, 71% of patients with Shigella gastroenteritis had more bands than segmented neutrophils in their peripheral white blood cell count.[131] However, this was also noted in 22% of patients with diarrhea due to Salmonella or *E. coli.*

Treatment

Treatment of shigellosis is indicated if the diagnosis is made early in the course of illness, as well as in certain hosts at high risk for septicemia and other extragastrointestinal complications. This includes newborns, patients with severe malnutrition, immunosuppressed patients, and those with hemoglobinopathies including sickle-cell anemia. Knowledge of the susceptibility pattern of Shigella in the community is essential for the initial prescription of effective therapy. For example, a recent outbreak of shigellosis associated with many deaths in Zaire was due to *Shigella dysenteriae* resistant to ampicillin, chloramphenicol, sulfonamides, and tetracyclines.[133] Plasmid-mediated multiple antibiotic resistance of this type can spread quickly through a community and cause many problems.

Eighteen cases of Shigella resistant to trimethoprim-sulfamethoxazole have also been reported.[125]

Complications

Some of the complications of shigellosis are described in Table 6–10. Shigella bacteremia with focal infections is a particular threat to infants and children with malnutrition, dehydration, and immunosuppression.[103] In these patients, there is often leukopenia, rather than leukocytosis and little or no fever. Shigella infections need to be taken seriously, in consideration of antibiotic resistance, their invasive nature, and the potential for extragastrointestinal spread and mortality in selected hosts.

Yersiniosis

Although Yersinia infections are frequent and well-described in some countries of the world, they are less common in others. The manifestations of Yersinia infection are diverse. Young children most commonly develop acute febrile diarrhea syndromes after primary infection with these bacteria, whereas children over 5 years of age often present with fever and abdominal pain. Diagnosis of Yersinia should be based on culture of the bacteria, since there are serious limitations in the use of serologic methods (agglutinins) in infants and in immunosuppressed patients, and cross-reactions with Brucella and autoantibodies are common.[50]

Epidemiology

Outbreaks of yersiniosis have become commonplace in North America, where infection with Yersinia previously was considered rare. Some Yer-

TABLE 6–10. Extragastrointestinal Complications of Shigella Infections

Septicemia[103]
Splenic abscess[367]
Hepatitis[369]
Hemolytic-uremic syndrome[144]
Vulvovaginitis[92]
Keratitis[329]
Meningitis[24]
Pneumonitis[24]
Postinfectious arthritis[24]

sinia outbreaks in rural areas are attributable to contamination of milk products.[364] In other cases, nosocomial infections have been recognized. In one such recent outbreak, nine hospitalized patients apparently became infected by person-to-person spread.[308] These outbreaks may also occur in families and are not restricted to the classic pathogenic types, as illustrated by a recent outbreak in Canada due to biotype 1.[243]

Clinical Manifestations

In addition to the gastroenteritis syndrome described in the previous section, many school-age children with acute Yersinia infections manifest severe abdominal pain.[174] This feature of acute yersiniosis is also seen with infection by a related bacteria, *Yersinia pseudotuberculosis,* a common cause of acute abdominal pain associated with mesenteric lymphadenitis.[115] Indeed, the abdominal pain has been so remarkable that many of these patients have had appendectomies before the recognition of yersiniosis as the cause. *Yersinia enterocolitica* can also cause intussusception,[57] gastrointestinal ulcerations, and a clinical and histopathologic picture resembling ulcerative colitis or acute ileitis.[389]

Extragastrointestinal Manifestations

Many infectious and postinfectious clinical manifestations have been associated with Yersinia infection (Table 6–11). As in the case of infection with other enteric pathogens, there may be a predisposition to septicemia in patients with hemoglobinopathies and other predisposing and immunocompromising illnesses.[162] Septicemia is particularly prevalent in immunocompromised patients, but can also be seen in normal patients.[370]

Many complications of Yersinia infection are due to direct bacterial invasion of a specific tissue or organ. In other cases, the evidence that Yersinia participates in the pathogenesis of the condition is less clear. For example Yersinia have been implicated in some cases of glomerulonephritis, thyroid disease, and arthritis, although the evidence is retrospective and based only on serologic criteria. The known cross-reactivity of Yersinia with other microbial and host tissue antigens complicates interpretation of these reports.[257] Nevertheless, there is little doubt that the acute septicemic form of arthritis is associated with Yersinia infection, since the organism has been cultured from both the bloodstream and the joint fluid.[379] Postinfectious types of Yersinia arthritis are less clearly associated with Yersinia infections, although it is said that the presence of IgA antibody to Yersinia is strong evidence in favor of this association.[141] In many of these cases, the disease resembles rheumatoid arthritis and parallels exist with the arthritic syndromes seen in the convalescent stage of other enteric infections. In one report, 56% of patients with

TABLE 6–11. Extragastrointestinal Complications of Yersinia Infections

Enteric fever[47]
Septicemia[356]
Lymphadenitis[173]
Conjunctivitis[87]
Cellulitis[316]
Skin abscess[221]
Lung abscess/osteomyelitis[349]
Pneumonia[37]
Liver abscess[233]
Cholangitis[327]
Mycotic aneurysm[301]
Glomerulonephritis[132]
Myocarditis[5]
Hemolysis[51]
Erythema nodosum[93]
Thyroid disease[33]
Arthritis[141]

arthritic complications of acute Yersinia infections were of the HLA-B27 halotype.[96] Thus, genetic and acquired infectious factors may predetermine the expression of arthritis in some of these patients.

Treatment

The treatment of yersiniosis is fruitless when the infection is confined to the gastrointestinal tract in normal hosts. Indications for treatment of Yersinia gastroenteritis in other hosts are listed in Table 6–12. Extragastrointestinal septic complications should be treated aggressively with appropriate antibiotic therapy (Table 6–13). I prefer moxalactam 200 mg/kg/day, although trimethoprim/sulfamethoxazole, cefotaxime, or aminoglycosides may also be used. Surgical drainage may also be necessary in some cases.

Cholera

Epidemiology/Pathogenesis

Vibrio cholerae infection most frequently manifests as acute diarrhea, and is one of the major causes of gastroenteritis in developing countries. The current pandemic began in 1961 in Indonesia, and has since spread to

TABLE 6–12. Indications for Antibiotic Therapy of *Yersinia enterocolitica* Gastroenteritis

< 3 months of age
Leukemia/lymphoma
Acquired or congenital immune deficiency disease
Moderate/severe malnutrition
Thallasemia
Appendicitis
Ulcerative colitis or other inflammatory bowel disease
Associated symptomatic intestinal parasitosis

many countries in Asia, Africa, and Europe. Foci in Texas and Louisiana have been identified, where transmission via gulf waters has been documented.[178] More frequently, infection in the United States is noted after travel to endemic countries.[363]

Man is the only host for *Vibrio cholerae,* and spread is maintained by contamination of water sources and, to a small extent, by chronic biliary carriage and stool excretion. Highest attack rates are seen in children between the ages of 1 and 5 years.[64]

The bacteria remain localized to the gastrointestinal tract in almost all cases. Disease is caused by release of a potent enterotoxin leading to fluid and electrolyte secretion into the lumen of the bowel, with consequent dehydration and metabolic imbalance.[64]

Other Vibrio species can also cause gastroenteritis[320] and a wide spectrum of clinical infection.[17]

TABLE 6–13. In Vitro Susceptibilities of *Yersinia enterocolitica*[344]

- Highly susceptible to
  - Cefotoxine
  - Moxalactain
  - Trimethoprim/sulfamethoxazole
  - Aminoglycosides (gentamicin, amikacin, tobramycin)
- Moderately (or variably) susceptible to
  - Kanamycin
  - Tetracycline
  - Chloramphenicol
  - Rifampin
- Resistant to
  - Ampicillin
  - Erythromycin
  - Penicillin
  - Cloxacillin
  - Cephalothin
  - Carbenicillin

Clinical Manifestations

Cholera is manifest by the abrupt onset of painless, watery diarrhea and vomiting. All degrees of illness are seen, including hypotension, cardiovascular collapse, and severe muscle cramps due to electrolyte depletion in far-advanced cases.

Diagnosis

The epidemiologic history and clinical characteristics are important. Fecal leukocytes are absent when the stool is examined microscopically; however, abundant numbers of Vibrio-shaped organisms may be seen with gram or methylene blue stain. Confirmation of the diagnosis is made by culture of *Vibrio cholerae* on thiosulfate-citrate-bile salt-sucrose (TCBS) agar.

Treatment

Replacement of water and electrolytes is of paramount importance. This can usually be accomplished by the oral route. Specific therapy for shock may be indicated as well. Bacterial excretion is reduced by the administration of tetracycline in a dose of 30 mg/kg/day, divided 4 times daily for 3 days. Doxycycline 4 mg/kg/day in a single oral dose is also effective.[330]

Prevention

Improvements in sewage disposal and the quality of drinking water are important, and public health measures have been instrumental in curtailing large outbreaks. Immunization may also be effective in endemic areas, as discussed in Chapter 1. Since the adherence of *Vibrio cholerae* to gastrointestinal epithelial cells is inhibited by IgA antibody, breast-feeding is an important method of preventing this disease in early infancy.[227]

Giardiasis

The diagnosis and management of acute giardiasis, as well as the chronicity of diarrhea in some cases, and the propensity for spread of disease in day-care centers, have been discussed in the section on gastroenteritis. Some other aspects of Giardia infection are described below.

Epidemiology

Giardia is considered to be the most common intestinal parasite in the United States and in Great Britain.[84] For example, infection rates of 30–

90% were found in recent surveys of day-care centers in New Orleans.[84] Children who wear diapers, many of whom are asymptomatic,[128] are particular reservoirs for this organism in closed populations. Person-to-person transmission and foodborne[282] and waterborne[108] spread have been reported. Other hosts likely to acquire Giardia frequently are selected populations of homosexuals and patients with altered intestinal immunity and hypogammaglobulinemia.[225] Treatment in the latter group may need to be prolonged, since control of symptoms may not be associated with eradication of the parasite.

Clinical Manifestations/Treatment

The younger the patient, the more likely he will be symptomatic. Most patients under 1 year of age who have Giardia organisms in their stools have diarrhea, often with symptoms of poor growth.[84] Chronic urticaria is a rare association.[155] Diarrhea, vomiting, anorexia, and failure to thrive are very common in children under 5 years of age. Because of this, it is recommended that Giardia infection in this age group should be treated in all cases. Those over 5 years of age usually have more abdominal cramps and may have intermittent loose stools and constipation. The natural course of illness in older children and adults is often 4–6 weeks, during which the stools become normal. In some patients, the course may be more chronic with intermittent abdominal pain, occasional loose stools, and malabsorption. Malabsorption may include the inability to absorb antimicrobials and other drugs.[84]

Furazolidone 7 mg/kg/day, divided three times daily, should be given for at least 7–10 days (Chapter 2). Shorter courses are prone to relapse.[267]

Complications

Other complications of giardiasis are listed in Table 6-14. Mesenteric lymphoid hyperplasia is sometimes visualized if these patients are treated surgically. Allergic reactions to Giardia have manifest as urticaria with associated eosinophilia and increased serum concentrations of IgE; occasionally, giardiasis is found in patients with asthma. Although unproven in controlled studies, it has been claimed that successful treatment of giardiasis in these cases reduced the frequency of asthmatic attacks.

Prevention

It is difficult to eradicate the parasite from human reservoirs and infected water supplies. Chlorination of water is generally ineffective without loss of palatability. Passage through a filter with a pore size less than 3 μm is usually necessary to eliminate the organism. In family units and in the community, careful handwashing and disposal of soiled diapers will help prevent spread.

TABLE 6–14. Complications of Giardiasis[84]

Chronic diarrhea/abdominal pain/failure to thrive
Malabsorption
Protein-losing enteropathy[358]
Biliary tract obstruction
Mesenteric lymphadenitis
Exercise-induced diarrhea
Peripheral neuropathy
Urticaria
Ulcerative colitis[399]

Amebiasis

Epidemiology

It is estimated that approximately 10% of the world's population is infected with *Entamoeba histolytica*, the causative parasite in amebiasis.[201] In some countries the figure may be as high as 30%. This includes some areas in the southwestern regions of the United States and Central America. Recently, amebiasis was the fourth leading cause of death in Mexico City.[254] The diagnosis needs to be sought aggressively and early. It should be considered high among the differential diagnoses of dysentery and extragastrointestinal febrile illnesses in patients recently living or traveling in endemic areas. The vast majority of cases are water-borne, but person-to-person spread has been noted in institutions for the mentally retarded and in family units.[109] Recently, 36 cases in the United States were transmitted by colonic irrigations.[172]

Clinical Manifestations

Amebiasis may take many forms. The commonest is asymptomatic infection, with or without a mild diarrhea syndrome at the onset. Uncomplicated colitis with mild dysentery is the rule, after an incubation period ranging anywhere from 1 to 8 weeks. Some patients, thereafter, become free of the parasite; others develop ameboma, which are tumorous lesions of the colonic mucosa, and others become asymptomatic cyst excretors. All of these should be treated.

The disease in infants may be more difficult to diagnose and may be extremely fulminant. In a recent series, two infants ages 6 and 7 weeks died quickly with an infantile disseminated form of amebiasis.[109] In this form of disease, diarrhea is followed by amebic infection of the liver, peritoneal cavity, and sometimes, pericardium.[119] Hematochezia, dysentery with appendicitis, and exacerbation of ulcerative colitis (or a true amebic ulcerative colitis) may also be seen in infants and children.[254]

Extragastrointestinal Amebiasis

Although invasion beyond the gastrointestinal tract occurs in less than 1% of patients with amebiasis, the diagnosis is often difficult and the outcome can be disastrous. Liver abscess is the most frequent extragastrointestinal manifestation. Colitis is usually present, but may not be obvious in many cases, unless sigmoidoscopy is performed. Fever and hepatomegaly are the most common presenting features; however, anemia, leukocytosis with a left shift, and elevation of the right hemidiaphragm are frequently present.[158] Infants are particularly prone to extragastrointestinal invasion. Hence, in a recent review of amebic liver abscesses, most of the children were under 3 years of age.[151] Remarkably, two-thirds of these presented with cough or breathing difficulty.

Other extragastrointestinal manifestations of amebiasis include peritonitis, pleuritis, pericarditis,[119] and, less frequently, lung and brain[166] involvement. Most of these occur as a result of direct extension from the gastrointestinal tract or liver to adjacent structures. Thus, skin lesions often are perianal or involve the genitals. Rarely, this disease can be spread by sexual contact; this may be more frequent in homosexuals. Colitis is one of the most important manifestations of amebiasis. If this is mistaken for ulcerative colitis in patients with underlying amebiasis, it may be disastrous.

Diagnosis

Fresh stools are often necessary for visualization of the trophozoites; however, concentrated specimens can be used to find cysts, the most common form in asymptomatic excretors. Formalin kills trophozoites, hence both examinations are necessary. It is important to realize the trophozoites and cysts may not be present in the stool of some patients, despite the presence of colonic lesions due to amebiasis. Serology and direct visualization of colonic or rectal mucosal lesions may be required for the diagnosis. When the latter procedures are carried out, fresh wet preparations of suspicious lesions and biopsy specimens should be examined.[201] Some practice is necessary in reading stool and tissue preparations for the presence of amebae. Misdiagnoses are common, since leukocytes may be mistaken for trophozoites.[208]

Liver abscesses should be more easily diagnosed with refinements in scan techniques. Radioisotope-labelled scans, ultrasonography, and computerized axial tomography can all be used. The latter is probably the most sensitive method available and can be used to diagnose liver and spleen abscesses due to bacteria, parasites, and fungi.[26] Infants, immunocompromised patients, and patients with heavy infestations and persistent signs should receive this examination. Most patients with hepatic liver abscess also have indirect hemagglutination antibodies.[97]

Therapy

Therapy for amebic dysentery and cyst excretors is discussed in the section on gastroenteritis. Extragastrointestinal amebiasis should be treated with metronidazole 35–50 mg/kg/day, divided three times daily × 10 days. When large liver abscesses or other complications (i.e., peritonitis, pericarditis, pleuritis) are present, dehydroemetine in a dose of 1.5 mg/kg/day (maximum 90 mg) should be administered intramuscularly once daily for 5–7 days as well.

The response to medical therapy is usually dramatic, with a reduction in fever and toxicity within 24–48 h. By 5 days, most patients have recovered. If not, persistence of signs in the presence of a focal abscess should suggest the need for aspiration and drainage. Open surgical drainage may be required if reaccumulation occurs after needle aspiration.[1] Large painful hepatic lesions, or leaking or fluctuant lesions, should be treated surgically as well as medically.

Diagnostic and therapeutic methods of control are improving the outlook for amebiasis, as is hygiene and improvement in sanitation and drinking water. Nevertheless, this infection remains ubiquitous and can be highly virulent in young infants and debilitated hosts. Confusion with inflammatory bowel disease can readily occur, particularly in patients with fulminant gastrointestinal amebiasis in countries with low endemicity.[74]

Stomatitis

Inflammation of the oral cavity is often a component of pharyngotonsillitis, exanthematous communicable diseases, and noninfectious conditions. When ulcers or vesicles are present, several specific syndromes come to mind. Glossitis has many causes, including local trauma, moniliasis, and acute *Haemophilus influenzae* infection.[112] Gingival lesions due to group A Streptococcus may appear cyst-like in young infants.[289]

Acute Stomatitis

Herpes Simplex in Normal Hosts. The causes of acute stomatitis are diverse (Table 6-15). In preschool children, herpes simplex is probably the most common cause of diffuse stomatitis. The tongue, gingiva, and often the lips, are also involved. Since these lesions are quite painful, the patient may be very irritable and may refuse to eat. Fever is often present, with temperatures in the range of 39–40°C for 3–5 days, and toxicity can be significant. Rarely, patients have lesions extending into the trachea and may require hospitalization for respiratory support; others need parenteral hydration and nutrition. The clinical course is generally between 1 and 2 weeks, during which time considerable weight loss may occur.

TABLE 6–15. Causes of Acute Stomatitis

Herpes simplex virus
Herpangina
Hand, foot, and mouth disease (coxsackie A virus)
Varicella zoster
Candida and other superinfections
Erythema multiforme
Drugs
Chemical burns
Collagen-vascular diseases (e.g., Lupus erythematosus)
Neutropenia
Aphthous ("canker sores")—first attack

In older patients, weight loss and fatigue are particularly troublesome components. Although topical anesthetics (such as lidocaine), ice chips, ice cream, and antiviral drugs, have been used, they rarely decrease the clinical course or significantly reduce viral excretion. Moreover, systemic toxicity (seizures) has been reported with the use of topical lidocaine.[259] Nevertheless, the patient with severe lesions may obtain some relief with one of these approaches. Oral acyclovir may be effective in reducing viral excretion and clinical illness, but experience with this treatment is limited.

Herpes Simplex in Immunocompromised Hosts. Primary herpes infection in immunocompromised patients is probably more dangerous then reactivation, as systemic dissemination may be more frequent and severe. In either case, this condition, like varicella zoster infection, requires treatment with systemic antiviral drugs. Both vidarabine and acyclovir are effective.[395] Acyclovir is used in a dose of 30 mg/kg intravenously, divided q 8 h. The drug is continued for 7–10 days or for approximately 2 days after resolution of the active lesions.

Varicella Zoster. Patients with chicken pox often have ulcerations on the palate, and, occasionally, on the buccal mucosa. These are generally of no consequence. When the patient is immunocompromised, extensive mucosal lesions suggest an increased risk for visceral spread. Antiviral chemotherapy, as suggested above for herpes simplex stomatitis, should be instituted.

Other Causes of Stomatitis. Other infectious causes of acute oral ulceration include the hand, foot, and mouth syndrome, usually due to coxsackie A virus, although enterovirus 71 has also been described as causative.[171] Although vesicular lesions are generally present on the hands and feet, this is not always so.

Rarely, staphylococcal or anaerobic infections of areas of traumatized mucosa may lead to ulceration and focal infection. Appropriate smear and culture examinations may provide a clue to the infectious etiology. Good oral hygiene usually suffices as treatment. When lesions are extensive or progressive, specific antimicrobial therapy should be instituted. As noted in Table 6-15, noninfectious causes may also be responsible for acute stomatitis. The first indication of the presence of inflammatory bowel disease may, in fact, be oral ulcerations.

Herpangina. Ulcers on the tonsil or in the peritonsillar area may be due to coxsackie A virus. These are often extremely painful. Occasionally, this may be due to herpes simplex virus.[238] This should be kept in mind if the patient is immunocompromised, as discussed above.

Candidiasis (moniliasis, oral thrush). The management of mouth ulcers and plaques due to Candida overgrowth is twofold. One is to try and discontinue use of the offending antibiotic or other predisposing factor. The other is the use of oral nystatin, clotrimazole, or other topical antifungal preparations. Repeated administration by swab or mouth rinse is needed. In severe cases, this should be done at least before every meal and at bedtime. When this occurs in immunocompromised hosts, or when esophagitis is present, or both, although systemic treatment with ketoconazole is preferred, clinical improvement is expected in only 5% of patients and eradication of Candida in only 36%.[167]

Recurrent Stomatitis

Aphthous Ulcers (canker sores). Although commonly believed to be due to herpes simplex virus, this is, in fact, rarely the cause of recurrent stomatitis, except in immunocompromised patients. Unfortunately, the commonest cause of recurrent single or multiple oral ulcerations is idiopathic (aphthous ulcers). Although they may have no cause, they certainly are painful! They may be single or multiple, but are generally confined to the buccal mucosa and lips. Occasionally, they are more extensive, even involving the trachea. The pathogenesis of this condition is unclear, although autoimmunity (the demonstration of antibodies against mucosal antigens), and mucosal injury in genetically predisposed hosts have been postulated.[411] Treatment of this condition is entirely symptomatic. Topical steroids (administered as mouth rinses or gargles), or a mouth wash consisting of combinations of tetracycline and amphotericin, have been used.[95] Although controlled trials suggest that these therapeutic practices are efficacious, the exact cause of the condition and pathognomonic laboratory findings are lacking. Hence, other causes of recurrent ulcerations should be ruled out (Table 6–16).

TABLE 6–16. Classification of Recurrent Stomatitis

- Aphthous (idiopathic)—"canker sores"
- Cicatricial pemphigoid
- Pemphigus vulgaris
- Lichen planus
- Pernicious anemia
- Ulcerative colitis
- Crohn disease
- Celiac sprue
- Behçet syndrome
- Herpes simplex
- Erythema multiforme[31]

Noninfectious Causes Including Behçet Syndrome. Among the causes of recurrent stomatitis (Table 6–16) are primary skin or mucosal disorders.[34] Inflammatory bowel disease, collagen-vascular diseases, and Behcet syndrome may also present as recurrent stomatitis. Behçet syndrome is rare in childhood, but has been described in a patient as young as 2 years.[266] This condition is manifest by febrile episodes associated with painful recurrent mucous membrane ulcerations, genital ulcers (of the penis, scrotum, vagina, vulva), skin involvement (erythema nodosum, pyoderma), eye inflammation (iritis), arthralgia, arthritis, and central nervous system involvement (meningitis, intracranial hypertension, dementia, encephalopathy). Occasionally, colitis has also been noted. The recurrent nature of these conditions, associated with aseptic meningitis, should suggest the diagnosis. The CSF usually has < 200 cells/mm^3 of mixed neutrophilic and mononuclear character; CSF protein concentration may be slightly elevated, but the glucose is normal and cultures are negative. The cause is unknown and there is no specific treatment. The more extensive the CNS involvement is, the poorer the prognosis.

Esophagitis

Pathogenesis

Infections of the esophagus are rare. They are occasionally seen postoperatively, where Staphylococcus species or anaerobic upper respiratory flora may be involved. In such cases, definitive diagnosis may be obtained by directly visualizing the lesion and obtaining appropriate smears and cultures. Antibiotic therapy is fairly straightforward. This is a very rare complication of modern approaches to esophageal surgery or trauma.

Etiology

The majority of patients who develop infections of the esophagus are debilitated in some fashion. Hence, both herpes simplex and *Candida albicans*, the leading infectious causes of esophagitis, have been described in patients with severe malnutrition, congenital and acquired immunodeficiencies, and posttraumatically. However, both infections may be seen in normal children as well. In fact, a healthy 10-year-old was recently described with herpes simplex esophagitis.[30] In such a case, the condition is often associated with oropharyngeal and gingival primary herpes stomatitis. This has also been described with *Candida albicans* infections in normal children and in patients with chronic mucocutaneous candidiasis, where both laryngitis and esophagitis were present.[202] Esophageal tuberculosis has also been reported.[152]

Diagnosis

Because the management of herpes simplex and of *Candida albicans* infections are so different, aggressive approaches to diagnosis are necessary. Clinical clues include fever, pain on swallowing, and retrosternal discomfort. When the patient has severe underlying disease, such as lymphoma or leukemia, or is known to have an immunodeficiency syndrome, including chronic mucocutaneous candidiasis, esophagoscopy and appropriate smears and cultures of suspicious lesions should be obtained.[181] Malignancy or immunosuppression have been associated with fatal outcomes, as recently noted for Candida esophagitis in a patient with leukemia.[180]

Radiographic demonstration of mucosal irregularities is the most consistent finding in esophagitis, although direct visualization through the endoscope is sometimes needed to see small lesions. Some clinicians prefer to use radiography and a clinical trial of ketoconazole therapy in a high-risk patient with severe underlying disease, thrombocytopenia, or other contraindications to endoscopy. However, even when the oropharyngeal surfaces are covered with lesions due to Candida, the possibility of a treatable herpes simplex esophagitis cannot be ruled out. We, therefore, prefer to administer platelets and proceed with endoscopy and definitive microbiologic diagnosis.

Treatment: Candida Esophagitis

Candida albicans esophagitis has been treated with a variety of topical antifungals in viscous and other vehicles. The approach to these patients has been revolutionized by the introduction of oral ketoconazole.[142] This drug in a dosage of 5–10 mg/kg/day, given as a single dose, is usually associated with symptomatic relief within the first week of therapy, except in the most severely affected individuals. Treatment should be continued for several weeks after resolution of the clinical and microbiologic features of the disease. In patients with chronic mucocutaneous candidiasis, treatment needs to be continued indefinitely. Nonetheless, this is a major advance in the treatment of these patients. One should look for emergence of resistant organisms, side effects of ketoconazole therapy, and other manifestations of the underlying disease. Intravenous amphotericin B may be required in resistant cases.

Treatment: Herpes Esophagitis

Acyclovir, 30 mg/kg/day, divided q 8 h, will generally effect cure of herpes simplex esophagitis within 7–10 days. This is a rare diagnosis, but a potentially fatal one. When the host is immunocompromised, it becomes even more important to diagnose and treat this condition very aggressively. Adequate precautions should be taken to limit exposure of high-risk contacts to patients with oropharyngeal herpes simplex infections with or without esophageal involvement.

Tuberculosis

Tuberculosis has also been described as a cause of esophagitis. Diagnosis depends on a high degree of suspicion and specific endoscopic and microbiologic findings. Treatment is the same as for systemic tuberculosis.

Complications

Rarely, patients with esophagitis may have perforations that lead to mediastinitis. In such cases, toxicity is marked, and high fever, severe retrosternal pain, and respiratory embarrassment are often present. This is an acute medical emergency requiring aggressive and specific chemotherapy and drainage if purulent material is present.

Hepatitis

Hepatitis in newborns is discussed in Chapter 3, particularly with regard to the transmission of infection from mother to newborn. Control measures for individual cases, protection of high-risk susceptible individuals, and management of outbreaks are discussed in Chapter 1; indications, doses, and side effects of passive and active immunizations are included.

Epidemiology

Hepatitis may be a manifestation of systemic infection or infection localized to the liver. Examples of the former include the jaundice noted in patients with bacterial sepsis and urinary tract infection, as well as the occasional involvement of the liver in tuberculosis, brucellosis, histoplasmosis, gonorrhea, Q fever, and viremia (Table 6–17). The vast majority of isolated cases of hepatitis are due to hepatitis A and B viruses, as well as to a group of poorly characterized agents, currently designated as non-A, non-B. Rarely, two types of hepatitis may coexist.[406]

The relative frequency of the various causes of hepatitis varies according to age, socioeconomic characteristics, and other epidemiologic factors. In a recent survey in Stockholm, 30% of cases of hepatitis were due to type A, 46% to type B, and the rest, presumably, to non-A, non-B.[400]

Hepatitis A. Hepatitis A is spread predominantly by fecal-oral contact and has an incubation period of 15–40 days. Attendance at day-care centers is currently the most important single associated factor in the spread of this disease in North America, accounting for approximately 10% of cases;[392] this includes most symptomatic disease in adults as well. Common sources associated with fecally contaminated milk, food, and water may be responsible for large outbreaks.[52] Transfusion of hepatitis

TABLE 6–17. Classification of Hepatitis

- Acute hepatitis
  - Subclinical
  - Symptomatic
    - Nonicteric
    - Icteric
  - Fulminant
    - Hepatitis A
    - Hepatitis B
    - Hepatitis non-A, non-B
    - Other viruses
      - Cytomegalovirus
      - Herpes simplex
      - Coxsackie[214]
      - Adenovirus
      - Epstein-Barr virus
      - Yellow fever
      - Rubella
    - Toxoplasma infection
    - Brucella infection
    - Syphilis
    - Leptospira infection
    - Q fever (*Coxiella burnettii*)
- Chronic hepatitis
  - Subclinical: HB$_s$Ag carriers
  - Persistent: HB$_s$Ag in serum + portal triaditis
  - Active: HB$_s$Ag in serum + symptoms + hepatocellular necrosis

A-containing blood, donated during the brief viremic phase of the infection (approximately 2 weeks before illness), can, rarely, cause post-transfusion hepatitis.[362]

Hepatitis B. Hepatitis B is usually spread by blood and blood products, although sexual transmission is not uncommon, particularly among homosexual men. Dialysis and transplant patients are also at high risk.[117] However, dialysis does not usually present a risk for transmission of hepatitis A.[246]

Travel and a history of contact with hepatitis B are also frequently identified risk factors for infection with this virus. Occasionally, spread among classroom contacts[279] and wrestlers[190] has been noted. Residents of institutions for the mentally retarded have a high prevalence of illness and chronic carriage, probably related to living conditions.[405] The incubation period is 1–6 months and asymptomatic carriage is frequent. The prevalence of asymptomatic hepatitis of all types is partly responsible for the difficulties encountered in controlling these infections.

The Carrier State. There are an estimated 200 million cases of hepatitis B in the world at this time. Most of these are present in asymptomatic carriers.[384] Since hepatitis B has been identified in blood, CSF,[215] tears,[90] saliva, semen,[343] and even in the vesicle fluid of a patient with concurrent hepatitis B and herpes zoster,[272] opportunities for dissemination are great. Spread to and from individuals with certain occupations, such as dentists and oral surgeons, often presents a practical problem.[310] The attack rate among these individuals has been estimated to range from 1/40 to 1/400 exposures, although the majority of these are expressed as asymptomatic infection. A chronic carrier state has been described for non-A, non-B hepatitis as well. In one such case, the patient's serum remained infectious for chimpanzees over a 6-year period (even in the absence of elevated liver enzymes).[376] There is no carrier state for type A.

Non-A, Non-B Hepatitis. Drug addiction is a common finding in the histories of patients with non-A, non-B hepatitis; however, blood transfusions are frequently responsible in this group as well. Hemophilia presents a risk for both hepatitis B and non-A, non-B, with chronic liver abnormalities in as many as 8% of patients.[315]

Etiology

Viruses cause most cases of acute and chronic hepatitis,[160] although this organ can be affected by almost all microorganisms (Table 6–17). Some of the parasitic causes of liver disease are included in Table 6–18. Hepatitis B virus consists of four different subtypes, and it is likely that non-A, non-B hepatitis represents several different virus types as well.[164]

TABLE 6–18. Parasitic Infections of the Liver

Amebiasis
Toxocariasis (visceral larva migrans)
Echinococcosis
Schistosomiasis
Clonorchiasis and other liver flukes

Among these is included the delta agent, usually associated with HB_sAg, and almost always seen in drug addicts.[258] Occasionally, virulent virus infections can involve the liver and, in some cases, may be fatal. This has been reported for herpes simplex (in normal[239] and transplant patients),[114] coxsackieviruses,[239] and adenovirus.[365]

Clinical Manifestations

Over 90% of children with hepatitis are asymptomatic.[71] In others, malaise, weakness, anorexia, and vague abdominal pain are first noted. This may be followed by nausea and vomiting, weakness, weight loss, more severe abdominal pain, and jaundice (Fig. 6–3). Occasionally, diarrhea, chills, and fever herald a more acute onset. The clinical signs and symptoms usually do not permit differentiation between the different causes, although myalgia and pharyngitis may be more frequently seen with type A, and a maculopapular erythematous rash and arthralgia with hepatitis B. When the latter occurs in the preicteric phase, this is often due to immune complex-mediated disease and serum complement concentrations may be low. This, as well as aplastic anemia, have also been reported with non-A, non-B infection.[294] These patients can have frank arthritis and vasculitis with malignant hypertension. Children of all ages can be affected, as exemplified by an 8-month-old infant in whom the latter two signs were associated with biopsy evidence of chronic hepatitis.[311]

A papular erythematous, nonpruritic rash involving the face and extremities may also be seen with nonicteric hepatitis. This is called Gianotti disease and is often associated with lymphadenopathy as well[337] (Fig. 6–4). The identical syndrome may be due to Epstein-Barr virus[198], rather than hepatitis.[335]

The onset of hepatitis A is generally more abrupt than that of hepatitis B, although there is considerable overlap. When hepatitis becomes clinically evident by jaundice, serum bilirubin concentrations are usually above 3 mg/100 ml. In such cases, the presence of dark urine and chalky, lightly pigmented stools is often noted. Vomiting and dehydration may be prominent features in some of these patients. When these progress, fulminant hepatitis needs to be considered. This is extremely rare for all types of hepatitis, particularly type A. It may occur in up to 1% of cases

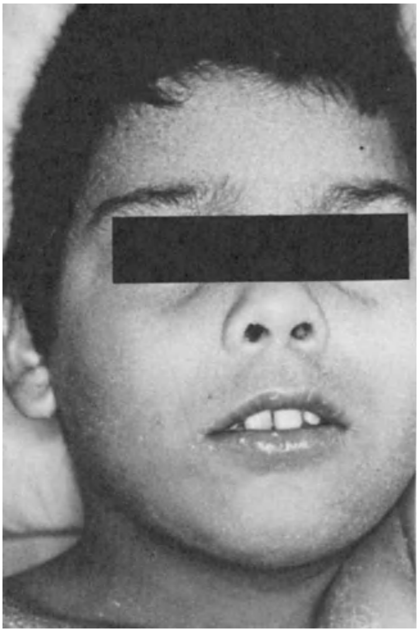

Figure 6–3. Scleral and cutaneous jaundice in patient with acute hepatitis. For color reproduction of this figure see frontmatter.

of type B, where the mortality rate is at least 80%. Deepening jaundice, encephalopathy, personality changes, somnolence, and progressive vomiting suggest this catastrophic event. Coma may then supervene. Physical examination in these patients may reveal hepatomegaly or a nonpalpable liver indicating severe hepatic necrosis. Liver tenderness is often marked in the early stages of hepatitis, but may be absent shortly thereafter.

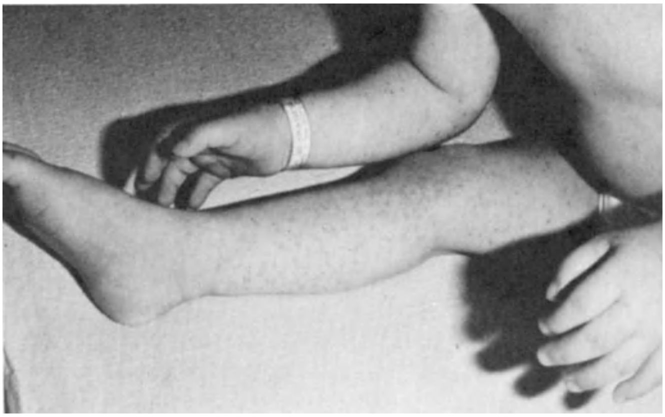

Figure 6–4. Papular acrodermatitis of Gianotti disease. For color reproduction of this figure see frontmatter.

Diagnosis

Hepatitis is most specifically suggested by scleral and skin jaundice, although sometimes fever, rash, and arthritis may be the only clinical signs. The most sensitive laboratory indicators of hepatitis are elevated concentrations of hepatocellular enzymes. Serum glutamic pyruvic transaminase (SGPT) (alanine aminotransferase) are most specific; however, hyperbilirubinemia (usually equal direct and indirect components), elevated concentrations of alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and lactic acid dehydrogenase enzymes are also present. The prothrombin time may be prolonged and the patient may not be able to metabolize many drugs that are normally cleared by the liver.

Etiologic diagnosis is critical to the management of hepatitis (Table 6–19). Hepatitis A can be diagnosed early by the detection of IgM antibody to this virus. This antibody may persist in the blood for up to 5 months.[392] A fourfold or greater rise of IgG antibody to this viral antigen is also diagnostic. Remember, IgG is passively transferred to newborns and can also be acquired via transfusion.

The serologic diagnosis of hepatitis B is complicated by the fact that the host responds to both surface and core antigens, and not always in a predictable fashion. Finding hepatitis B antigen in the serum of a patient indicates either acute disease or the carrier state. The presence of antibody to hepatitis B surface or core antigens indicates acute infection or

TABLE 6–19. Serodiagnosis of Hepatitis

Acute hepatitis A	Anti-HAV IgM Fourfold or greater rise in anti-HAV IgG
Hepatitis A: Past infection or passive immunization	Anti-HAV IgG
Acute hepatitis B	HB$_s$Ag (see chronic hepatitis also) Fourfold or greater rise in anti-HB$_s$ or anti-HB$_c$ Anti-HB$_s$
Hepatitis B: Past infection or passive immunization	Anti-HB$_s$ ± anti-HB$_c$
Chronic carrier hepatitis B	HB$_s$Ag > 6 months
Chronic persistent hepatitis B	HB$_s$Ag > 6 months + elevated liver enzymes
Chronic active hepatitis B	HB$_s$Ag > 6 months + elevated liver enzymes + liver biopsy showing hepatocellular necrosis beyond the portal triads
Immune response to vaccination	Anti-HB$_s$

previous infection with these viruses; however, fourfold rises of either of these antibodies in appropriately timed acute and convalescent sera are diagnostic of recent infection.[7] Occasionally, hepatitis B surface antigen can disappear from the blood during fulminant hepatitis. This may be due to a presence of an excessive amount of antibody.[375] The presence of IgM antibody to core antigen (anti-HBc IgM) may also distinguish acute type B hepatitis from past infection with this virus.[216]

Liver biopsy is not usually needed for diagnosis, but can suggest the etiology or prognosis of hepatitis. Widespread granular swelling of hepatocytes, so-called ballooning, is characteristic of acute viral hepatitis. Precise dating of a lesion is not possible, but in latter stages cellular necrosis subsides and phagocytosis and portal infiltrates predominate. In chronic persistent hepatitis, there is minimal hepatocellular necrosis and lymphoplasmacytic inflammation is limited to portal tracts. Chronic active hepatitis features more widespread inflammation and necrosis, particularly at the interfaces of liver cells and connective tissue.

Granulomatous hepatitis can result from a wide variety of infectious (e.g., mycobacteria, histoplasma, parasitic) and noninfectious (e.g., sarcoidosis, drug-induced, immune deficiency) causes.[157]

Treatment

There is no specific treatment for acute hepatitis other than supportive care. The patient is often weak and may be dehydrated. Drugs, including alcohol, that are metabolized through the liver should be avoided, as should severe physical and emotional stress. Corticosteroids do not help.[396]

The patient with progressive hepatic injury in the acute stage will require management of the complications associated with liver failure.[16] In such cases, neomycin is given orally and by enema to reduce the load of intestinal bacteria and absorption of their metabolic products. Vitamin K, electrolytes, and fluids, as well as a low-protein diet, are also prescribed. There is little to suggest that other specific therapies are useful. In one report interferon therapy was associated with improvement in three of five patients with fulminant hepatitis, but controlled studies are not available.[219] Heroic management of liver failure has included dialysis, exchange transfusion,[240] and cross-circulation experiments, in an effort to reduce circulating metabolic toxins in the affected individual. Management of acute renal failure, which may be due to tubular necrosis that accompanies liver failure, may also be indicated. The prognosis in such cases is extremely grave and death is usually due to bleeding, electrolyte disturbances, encephalopathy, or superinfection.

The treatment of chronic active hepatitis is still in the experimental stages. There is some evidence that interferon, or interferon plus adenine arabinoside, may benefit these patients;[345] however, adenine arabinoside has little effect when used alone.[28] Corticosteroids[211] and immunosuppressive therapy[386] are not useful.

Prognosis/Complications

Since hepatitis may be only one component of a systemic infection, extrahepatic complications are often present. Hence, patients with herpes simplex hepatic infection may also manifest skin and neurologic involvement, and adenovirus infection and tuberculosis often have pulmonary pathology. With hepatitis due to type A, type B, and non-A, non-B viruses, acute fulmination and chronic persistent and active hepatitis may occur.[305] These are least frequent in young children and in those with type A. Two percent of patients with hepatitis B and up to 25% of those with non-A, non-B disease may develop persistent or chronic active changes.[400] Patients with acute hepatitis may also have aplastic anemia,[418] pancreatitis, renal failure, pericarditis,[3] membranous nephropathy,[378] and central nervous system (CNS) manifestations, including meningoencephalitis.[54] Occasionally, the CNS manifestations may occur in the prodromal period, in which meningitis, peripheral neuropathies, myelitis, and encephalitis have been reported.[153] Although immunity is usually lifelong after recovery from infection, repeated episodes of hepatitis B due to different subtypes are possible.[373]

Chronic active hepatitis (as indicated by at least three times the normal concentration of serum transaminases for longer than 6 months) may be seen in some cases of hepatitis B even when serologic markers are not present.[390] The development of chronic hepatitis is a particular risk of leukemic children, occurring in one-half of children in a recent study.[231,390]

One of the most important complications of chronic hepatitis B infection is the development of hepatocellular carcinoma. Predominantly a complication seen in adults, hepatoma has also been noted in a child 7 years after perinatal infection.[32] Evidence for a causative role has been provided by the demonstration of the integration of hepatitis B viral DNA into liver cell genomes.[354] Although hepatocellular carcinoma is relatively infrequent in North America, it is the leading cause of death from cancer worldwide.

Prevention

Use of passive and active immunization for the prevention of hepatitis is discussed in Chapter 1 and, for newborns, in Chapter 3. Several points deserve emphasis. Hepatitis A outbreaks in day-care centers require aggressive action. Passive immunization of the students, day-care center employees, and adult members of the households of infants wearing diapers who attend day-care centers should be instituted quickly.[150] This is because the majority of the children who wear diapers will have asymptomatic infection, and spread is common among adults exposed to these children.[149] Since many of these children will be in the first 2 years of life, their active immunizations should be deferred for 3 months after the use of immune globulin. Fecal shedding of hepatitis A virus is most intense 1 week before and 1 week after peak elevation of serum glutamic pyruvic transaminase, but the reported range is from 19 days before peak to 25 days afterwards.[234] Moreover, hepatitis A virus may remain viable in dried fecal material for a month at room temperature.[247] These data should be considered in formulating isolation recommendations for fecally incontinent hospitalized patients with unexplained liver abnormalities. Such patients present an increased risk of nosocomial spread of hepatitis.[280]

Dentists and surgeons should use gloves, masks, and protective eye wear[310] to protect themselves from acquiring hepatitis B from their patients, and, if they are carriers, to prevent spread to their patients.

The frequency of spread of non-A, non-B hepatitis can be reduced (by approximately 30%) by screening donor blood for alanine aminotransferase concentrations[8]. Screening blood and blood products for the presence of hepatitis B surface antigen is also effective.

Parasitic Causes of Hepatitis

Several parasitic infections, such as amebiasis, are common worldwide and involve the liver as their primary target site (Table 6–18).

Toxocariasis. Toxocariasis (most frequently seen in 1–4-year-olds) is usually acquired by ingestion of infected dog and cat feces, or soil containing these materials. Sandboxes in playgrounds are a very high-risk site. Infected patients are usually asymptomatic, although a small number develop fever, cough, wheezing, and some also have weight loss and hepatomegaly. Pulmonary infiltrates may be present transiently. The diagnosis is most specifically suggested by the presence of hepatomegaly, eosinophilia, and elevated serum concentrations of IgE. The diagnosis can be confirmed by the measurement of Toxocara ELISA antibodies. Thiabendazole treatment is usually helpful (Chapter 2).

Echinococcosis. Echinococcus eggs are present in dog feces and may be ingested by young children. Hepatomegaly is the most prominent sign and is usually due to the presence of single or multiple cysts, most often in the right lobe of the liver. Eosinophilia is commonly present and lung involvement may also be apparent. Ultrasound, radioisotope scanning, or computerized axial tomography are most useful for diagnosis, which is confirmed by appropriate serology.[148] Treatment consists of surgical removal of the cyst, although mebendazole[194] (Chapter 2), and another benzimidazole-carbamate, albendazole,[332] may also be useful in selected cases.

Schistosomiasis. Schistosomiasis is prevalent worldwide and is acquired by young children in the toddler age group when they walk barefoot in water. The parasite is carried by fresh water snails whose eggs (cercariae) penetrate the skin. The first manifestation of this infection is often called "swimmer's itch," and is associated with a pruritic skin rash and hematochezia.[371] Subsequently, a serum sickness-like reaction may occur with a rash, fever, eosinophilia, and arthralgia. This is sometimes called "Katayama fever." In a very few patients, hepatomegaly and subsequent cirrhosis, portal hypertension, and splenomegaly occur.[397] The most serious threat to such patients is progressive liver failure with portal hypertension and hemorrhage from esophageal varices.[412] The diagnosis is made by detection of ova in stools, urine, or rectal biopsy (Fig. 6–5). Treatment consists of therapy with oxamniquine[371] or praziquantel (Chapter 2).

Liver Flukes. *Clonorchis sinensis, Opisthorchis viverrini* (seen in Russia and Southeast Asia), and *Fasciola hepatica* may also cause hepatic injury, most commonly manifest as cholangitis.[372] They are acquired by eating insufficiently cooked fish or meat. The diagnosis is made by visualization of eggs in the stool. No effective treatment is known, although praziquantel may prove useful in some cases (Chapter 2).

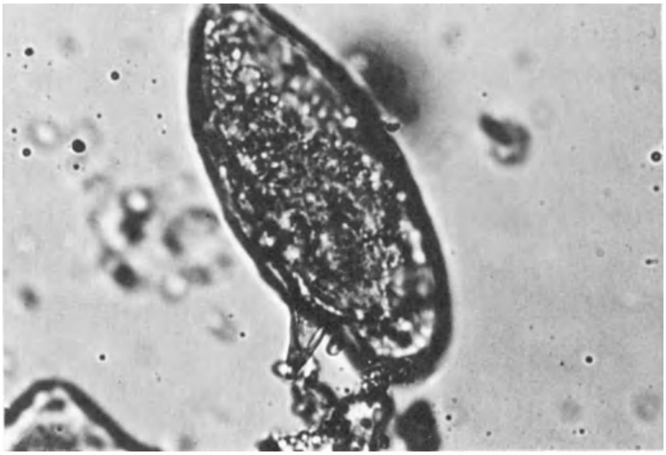

Figure 6–5. Ovum of *Schistosoma mansoni.*

Hepatic, Splenic, and other Intraabdominal Abscesses

Pathogenesis/Etiology

Intraabdominal abscesses are most frequently seen after peritoneal soiling due to rupture of the appendix or other viscus, secondary to inflammatory or traumatic conditions. Abscesses of the liver and other intraabdominal sites are seen after venous catheterizations, abdominal surgery, and in immunocompromised patients. The location of the abscess is often dependent on the source of the infection and the position of the patient. After diffuse peritoneal soiling, localization under the liver (subhepatic abscess) or under the diaphragm (subdiaphragmatic) can be seen. Although they are extraperitoneal, renal, adrenal, and other retroperitoneal abscesses have many of the characteristics of intraabdominal abscesses and the principles of diagnosis and management are the same.

No age group is immune to intraabdominal abscess formation; however, the condition is relatively rare at all ages. Newborns may be particularly susceptible because of their immunologic immaturity and their exposure to vascular cannulations and bacteremic episodes during intensive care. Enteric organisms, and Listeria, Pseudomonas, and Candida abscesses may be found in the livers of such patients.[265]

Patients with chronic granulomatous disease or leukemia may have staphylococcal liver abscesses or mixed infections, including anaerobic bacteria.[73] Intraabdominal sepsis after peritoneal soiling is commonly polymicrobial, and anaerobic bacteria are frequently involved.[25] Amoeba, parasites, such as echinococcus,[189] enteric bacteria, and streptococci[262] should be considered in the etiologic spectrum of microbes causing liver abscesses.

Splenic abscesses are unusual, only 11 cases being diagnosed over a 30-year period in a major United States medical center.[340] However, this diagnosis should be considered in patients who have been bacteremic, in individuals who abuse intravenous drugs, and in others who have appropriate symptoms. A variety of infections, including those with enteric bacteria, Staphylococcus, and *C. difficile* and other anaerobes may be involved.[331]

Clinical Manifestations

Fever, abdominal pain, and hepatomegaly are the major signs of hepatic abscess. Similar features are noted in association with left-sided pain when splenic abscess is present. Other causes of intraabdominal sepsis are more difficult to localize clinically; however, perirectal masses and tenderness may be present with pus collections in the pelvic area.[55] Shoulder tip discomfort may be a sign of subdiaphragmatic abscess, as may chest pain and respiratory signs. Anemia, fever of unknown origin, or gastrointestinal or urinary obstruction are occasionally the only signs.

Diagnosis

Modern noninvasive techniques such as radionuclide scans and computerized tomography have simplified the diagnosis of intraabdominal abscesses.[121] Ultrasonography or ^{111}indium-labelled leukocyte scans can also be used, although the latter technique is still investigational.[65] Confirmation of the etiology often requires percutaneous needle aspiration, laparoscopy, or laparatomy.

Treatment

The diagnosis of an intraabdominal abscess should prompt a review of the pathogenesis. Neglected appendicitis, other foci leading to bacteremia, or immunodeficiency may thus be found. The abscess itself should be aspirated by the percutaneous route in order to establish an etiologic diagnosis. This can be guided by ultrasonography[36] or computerized tomography.[388] These techniques can also be used to treat some of these lesions. In selected cases, however, laparatomy and more complete drainage are critical to therapeutic success.[391]

It is clear from a review of the etiology of intraabdominal abscesses that polymicrobial infections are common,[55] as are bacterial, parasitic, protozoan, and fungal causes. Blind therapy of these lesions is, therefore, fraught with hazard. Microbiologic, serologic, and histopathologic data are often essential for appropriate management. Antimicrobial therapy should usually be continued for approximately 4–10 weeks, with shorter courses made possible by complete drainage of the lesion.[293]

Cholecystitis

Pathogenesis/Epidemiology

Cholecystitis is uncommon in the pediatric population. As in adults, obese girls seem at higher risk,[11] as do pregnant individuals, particularly those with associated urinary tract infections.[348] Other predisposing factors include hemolytic diseases (e.g., sickle-cell disease and glucose-6-phosphate dehydrogenase deficiency) congenital anomalies of the biliary tree, pancreatitis, and traumatic liver injury.

Etiology

The incidence of cholecystitis without biliary calculi seems more frequent in children than in adults. In such circumstances, infection of the bile and gallbladder may be a complication of a systemic infection, such as scarlet fever,[98] leptospirosis,[27] or secondary to gastrointestinal infection. The bacteriology of acute cholecystitis in children is predominantly that of enteric bacteria, such as *E. coli,* Klebsiella, *Streptococcus faecalis,* and anaerobic bacteria. Patients with Salmonella infection, including typhoid, and those with mucocutaneous lymph node syndrome may also have gallbladder involvement in the early or late convalescent stages of their illnesses. Various causes of biliary obstruction, such as ascariasis, may also be responsible. Rarely, air in the biliary tract (emphysematous cholecystitis) may indicate the presence of infection due to gas-producing bacteria.[324]

Clinical Manifestations

Abdominal pain is marked in acute cholecystitis. Occasionally, a palpable mass in the right upper quadrant may provide a clue to the presence of cholecystitis or hydrops of the gallbladder. Nausea and vomiting are often present as well, but fever may be absent in two-thirds of cases.

Diagnosis

Although jaundice or subclinical hyperbilirubinemia is uncommon in patients with cholecystitis, patients with underlying liver or biliary tract disease may have persistent elevations of serum bilirubin and alkaline phosphatase. Patients with hemolytic diseases should also be carefully examined for the presence of biliary tract stones. Oral or intravenous cholecystograms may help confirm the diagnosis, as may ultrasonography or tomography.

Treatment

Cholecystectomy is the treatment of choice for this condition. Antibiotics are rarely needed, except if complications of surgery occur. In rarer circumstances where surgery is not possible, antibiotic therapy directed against enteric bacilli, such as combinations of metronidazole or clindamycin with aminoglycosides or cefoperazone, is useful. Kanamycin, amikacin, and cefoperazone penetrate into the bile and gallbladder wall particularly well.[156] Although cefamandole penetrates into bile,[309] this drug should be used only if specific microbiologic cultures (i.e., bile, gallbladder, or blood) demonstrate a susceptible causative organism. When cholecystitis is associated with calculi that cannot be removed, congenital anomalies of the biliary tract, cholangitis, or peritonitis, antibiotic therapy may be an important adjunct to biliary drainage.

Thus, cholecystitis is rarely a primary infection of infants and children, but more commonly presents as a complication of a congenital or traumatic condition, obstruction, calculi, hemolytic disease, or associated with systemic infectious or inflammatory diseases.

Cholangitis

Clinical Features/Pathogenesis/Etiology

The most common predisposing condition for recurrent cholangitis is portoenterostomy, often used to correct biliary atresia. These patients have nausea and vomiting, fever, shaking chills, paralytic ileus, or other signs of acute abdominal distress. Bacterial hepatitis may also be present. Because of this risk, trimethoprim/sulfamethoxazole and phenobarbital (to increase bilirubin conjugation and excretion) prophylaxis is often prescribed for 1 year after such an operation.[22]

Other factors that may predispose to cholangitis include acquired or congenital structural defects of the hepatobiliary system, generalized sepsis, and biliary tract stones and surgery. Underlying disease is not always present. For example, a normal 10-week-old presented with fever of unknown origin, hepatosplenomegaly, anemia, and increased partial thromboplastin time.[413] Liver biopsy provided the etiologic diagnosis, a useful procedure in the diagnosis of cholangitis. In this case, *Enterobacter agglomerans* was cultured, which was responsive to therapy.

Parasitic infestations, particularly infections with liver flukes (see Hepatitis), and, rarely, ascariasis may also present as cholangitis.

Diagnosis

It should be remembered that cholangitis in older patients is characterized by severe shaking chills, right upper quadrant pain, and occasionally, right shoulder pain. Nausea, vomiting, signs of acute abdominal injury, and jaundice may also be present. Diagnosis is made on the basis of blood cultures, abnormal liver function tests, and cholecystography. Computerized axial tomography or ultrasonography may show a dilated biliary tract or stones. If a liver biopsy is carried out, a blood culture obtained after biopsy may be useful, as organisms are often liberated into the systemic circulation by this procedure. Urine culture is useful in all cases of hepatic and biliary infection because of the possibility of associated urinary tract infection.

Treatment

Treatment of cholangitis is the same as described above for cholecystitis. Trimethoprim/sulfamethoxazole may be used in selected patients because of its excellent penetration into biliary tissue.[163] Remember, the majority of these patients have underlying diseases and control of cholangitis usually brings about dramatic, but temporary, relief, if the predisposing factors are not corrected. Patients with portoenterostomies, in fact, suffer from recurrent cholangitis, and liver failure may result unless effective drainage is carried out.

Pancreatitis

Pathogenesis

The pancreas may be infected in a variety of ways, none of which is very common. First, it may occur as part of a generalized process, as in mumps or coxsackie virus infections. This is much less commonly noted in bacterial infections, although patients with septic shock may have pancreatic involvement secondary to direct bacterial invasion, endotoxin, or hypoxemia.

Pancreatitis, with or without abscess formation, may also be associated with bacterial superinfections after trauma and surgery.

Finally, late complications of the direct effects of infection or an interplay of infectious agent and genetic, drug-induced, or autoimmune factors may produce diabetes mellitus. This is seen in congenital rubella[253] and, occasionally, after acquired mumps or coxsackie virus infections.[199]

Etiology

Some infectious and noninfectious causes of pancreatitis are listed in Table 6–20. The evidence for mycoplasma infections is serologic and caution is urged in accepting these case reports as proof of a direct causative relationship.[277]

Clinical Manifestations

Acute pancreatitis is most commonly heralded by severe abdominal pain. This may be referred to the back, the epigastrium, or the lower abdomen. Such pain, after abdominal trauma, is highly suggestive of pancreatic injury. Vomiting may also be present in both the acute and chronic forms of the disease. Complications of pancreatitis may lead to the presence of paralytic ileus, pleural effusions, or ascites.[184]

Diagnosis

The above clinical signs may be associated with an increase in the peripheral white blood cell count, hyperbilirubinemia, elevated or reduced serum concentrations of calcium, and hypercholesterolemia. Serum am-

TABLE 6–20. Causes of Pancreatitis

- Infectious
  - Mumps
  - Coxsackie
  - Cytomegalovirus[199]
  - Varicella zoster[199]
  - Epstein-Barr virus
  - Congenital rubella[253]
  - Ascaris
  - *Mycoplasma pneumoniae*[277]
  - Congenital syphilis
- Noninfectious
  - Corticosteroids
  - Drugs (azathioprine, L-asparaginase, furosemide, chlorthalidone, chlorthiazide)
  - Trauma
  - Hyperparathyroidism
  - Biliary tract disease
    - Congenital
    - Acquired
  - Scorpion bite
  - Reye syndrome
  - Diabetes mellitus
  - Cystic fibrosis
  - Idiopathic
  - Hyperlipoproteinemia

ylase and lipase levels are usually elevated. Although it is stated that serum amylase levels three times normal values are diagnostic, this may also be seen in occasional cases of parotitis, mumps, biliary disease, bacteremia, and abdominal trauma. Ultrasonography may demonstrate reduced echodensity of the pancreatic tissue or a pseudocyst.[83] Computerized tomography may also be useful when cysts are present.

Complications

As mentioned above, gastrointestinal and peritoneal complications have been noted, usually after traumatic pancreatitis. Sepsis and pancreatitis may also increase the risk of developing pancreatic abscesses, associated pneumonias, and peritonitis.

A late complication of pancreatic involvement by infectious pancreatitis may be the development of diabetes mellitus.[67] The pathogenesis is felt to involve pancreatic injury with formation of antibodies against pancreatic islet cell tissue and the development of diabetes mellitus several years later.[15] These autoantibodies have also been demonstrated in both coxsackie virus and mumps virus infections in the absence of pancreatitis.[159] Pancreatic abscess is a rare complication of septicemia or traumatic pancreatitis.[314]

Management

Pancreatitis is rarely diagnosed as an isolated illness. Generally, treatment is directed at the infectious cause, such as septicemia, or parasitic infection. In other situations, therapy may be directed at peritonitis, associated pneumonia, or, in rare cases, pancreatic abscess. In the latter instance, anaerobic bacteria and enteric organisms may be found as well as *Staphylococcus aureus*. Aggressive diagnostic procedures with appropriate microbiologic studies are indicated. Patients with pancreatitis associated with trauma, surgery, or biliary tract diseases rarely require antibiotic therapy. Pseudocysts usually contain sterile fluid filled with debris and digested tissue, and generally do not require antibiotic therapy or prophylaxis.

Peritonitis

Pathogenesis

There are several ways in which peritonitis may occur, and the microbiologic causes are extremely diverse (Table 6–21). Peritonitis is most commonly a complication of peritoneal dialysis or perforated bowel. Approximately 1/100–1/1000 dialysis episodes may be associated with peritonitis.[248] In part, this may be due to the fact that peritoneal dialysate may be inhibitory to polymorphonuclear phagocytosis and intracellular bactericidal activity.[107] Staphylococcal nasal carriers may also be at risk for dialysis-associated staphylococcal peritonitis.[351]

Many cases occur in situations where bowel perforation develops after appendicitis or after surgery. A rare exception is bowel perforation due to ventriculo-peritoneal shunt irritation.[350]

Primary peritonitis occurs in patients with ascites due to a wide variety of underlying conditions, including liver disease, nephrotic syndrome, and postoperative conditions. Normal subjects may also develop peritonitis, although this comprises < 1% of cases of acute abdominal infection.

Etiology (Table 6–21)

This infection, in patients undergoing peritoneal dialysis (many on a continuous basis at home), is sometimes referred to as "ambulatory peritonitis" (Table 6–22). Staphylococci account for 30–40% of infections

TABLE 6–21. Classification of Peritonitis

Type	*Most Common Infectious Agent*
Primary	*Streptococcus pneumoniae, Streptococcus pyogenes*
Bowel perforation	*E. coli, B. fragilis*, group D Streptococcus, *Candida*
Peritoneal dialysis	*Staphylococcus epidermidis, Staphylococcus aureus*, gram-negative enteric bacilli, Yeasts
Nephrotic syndrome	*Streptococcus pneumoniae, E. coli*
Other	
V-P shunt	*S. aureus, S. epidermidis*, gram-negative enteric bacilli
Septicemia	Variable
Tuberculosis	*M. tuberculosis*
Pelvic inflammatory disease	*N. gonorrhoeae, Ureaplasma urealyticum, Chlamydia trachomatis*, anaerobic bacteria. Actinomyces (with intrauterine contraceptive device). *S. pneumoniae* (with intrauterine contraceptive device).[145]

in these patients.[213] In one-third, sterile fluid is obtained, and, in some circumstances, peritonitis may be a response to endotoxin.[188] In others, atypical mycobacteria (*Mycobacterium chelonei*) may be responsible. In one particular outbreak, 5/22 patients undergoing intermittent chronic peritoneal dialysis acquired mycobacterial peritonitis by cross-infection through a contaminated dialysis machine.[20] *Candida albicans*[176] (and other species including *C. parapsilosis*),[217] *Drechslera spicifera*,[283] *Bordetella bronchi-*

TABLE 6–22. Infectious Causes of Ambulatory Peritonitis

Staphylococcus epidermidis
Staphylococcus aureus
E. coli
Pseudomonas aeruginosa
Anaerobic bacteria
Candida spp.
Aspergillus
Nocardia
Mixed

septica,[60] and Aspergillus and Nocardia[13] infections have also been described. Thus, the microbiology of ambulatory peritonitis is diverse indeed!

Infants and children with nephrotic syndrome may also develop peritonitis, particularly when ascites and hypogammaglobulinemia are present. In a recent review of 310 children with nephrotic syndrome, 24 episodes were documented in 19 children.[206] Thirteen were due to pneumococcus, five to *E. coli,* one to *Bacteroides fragilis,* and one to α-Streptococcus species. Others have reported streptococci, including group B Streptococcus,[21] and *Haemophilus influenzae.*[70]

In newborns undergoing gastrointestinal surgery the peritoneal cavity may be contaminated with *E. coli, B. fragilis,* and group D streptococci.[35] Fungal peritonitis may also occur after bowel perforation.[306]

Although less frequent today, tuberculous peritonitis is seen in countries in which tuberculosis is prevalent. These patients suffer from chronic abdominal pain and gastrointestinal dysfunction.[99]

Primary peritonitis (i.e., in normal hosts without a known predisposing condition) are usually due to pneumococci, streptococci, or enteric gram-negative bacteria. Anaerobic bacteria (e.g., *Fusobacterium necrophorum*) may rarely be causative,[245] as may *Clostridium perfringens*[409] and *Haemophilus influenzae.*[138]

Clinical Manifestations

Peritonitis is characterized by diffuse abdominal distension and, sometimes, a rigid abdomen. In many of these cases, rebound tenderness is obvious and bowel sounds may be reduced or absent. Fever, ascites, vomiting, and, occasionally, diarrhea, may also be present. In some cases, the abdominal pain may be severe enough to mimic appendicitis. Pneumoperitoneum (demonstration of gas in the peritoneal cavity) may indicate bowel perforation or the presence of *E. coli*[302] or *Clostridium welchii.*[361]

Diagnosis

When the above clinical signs are noted, a plain radiograph of the abdomen may reveal free air or paralytic ileus. Aspiration of peritoneal fluid is the next step. Gram stain may reveal the causative organism, although yeasts may also be seen in unstained wet preparations. Cultures should be appropriate for aerobic and anaerobic bacteria, as well as for fungi and, in selected cases, acid-fast bacilli. Peritoneal biopsy may be useful in cases with more chronic presentations and where tuberculosis is suspected. Finding peritoneal granuloma raises an interesting, albeit rare, differential diagnosis (Table 6–23).

In patients receiving peritoneal dialysis, examination of the dialysate

TABLE 6–23. Causes of Granulomatous Peritonitis

Tuberculosis
Histoplasmosis
Coccidiomycosis
Blastomycosis
Cryptococcosis
Candidiasis
Actinomycosis
Nocardiosis
Syphilis
Brucellosis
Tularemia
Foreign body reactions (e.g., talc)
Hypersensitivity (e.g., beryllium)

for the presence of leukocytes and bacteria can be very helpful.[200] An increase in the number of leukocytes should prompt early therapy for staphylococci, unless the gram smear suggests other etiologies. Cultures should be obtained in all cases and antimicrobial therapy adjusted appropriately.

Treatment

Treatment is generally guided by the results of the gram stain and, later, by microbiologic culture. Nonetheless, several clues can be provided by knowledge of the most likely etiologies of the various forms of peritonitis (Table 6–21). Hence, antistaphylococcal therapy is indicated early for treatment of peritonitis in patients receiving peritoneal dialysis. Neonatal peritonitis associated with gastrointestinal perforation can be treated with combinations of ampicillin, gentamicin, and clindamycin, in consideration of the bacterial flora found in many of these cases.[35] The cornerstone of treatment of bacterial peritonitis due to bowel perforation in individuals of all ages includes early surgery to repair the leak, debridement of necrotic tissue, and drainage of any abscesses that are present. Peritoneal lavage with or without antibiotics seems to add little to these procedures.[169] Parenteral antibiotic therapy is usually adequate, since most drugs diffuse extremely well into the inflamed peritoneal cavity. For example, approximately 68% of the serum concentration of gentamicin was found in the peritoneal fluid in such patients in a recent study.[312] Those considering using povidone-iodine for lavaging the contaminated peritoneal cavity should pay heed to the mortality associated with this procedure in experimental peritonitis in dogs.[48] Remember, the peritoneal surface is extremely large and absorptive, and aminoglycosides, iodine, and other substances may rapidly reach the systemic circulation.

Patients receiving peritoneal dialysis present some special problems[248] as a result of the diversity of causes and the presence of the dialysis catheter. When the catheter malfunctions, it must be removed. In other cases, early effective antibiotic therapy may avoid the need to remove the catheter. The most frequent bacterial causes of peritonitis in patients receiving dialysis can be treated early by adding antibiotics to the dialysis fluid.[124] In general, most antibiotics, such as cephapirin, gentamicin, nafcillin, ticarcillin, and vancomycin are stable for 24 h at room temperature in dialysis fluid.[352] This may be a problem with penicillin, however, since approximately 25% of activity is lost during this period of time. Systemic antibiotics can also be used,[200] as most β-lactams enter the peritoneal fluid easily.[408]

Although early therapy is directed against the common bacterial causes (Table 6–21), the possibility of yeast infection should also be kept in mind.[306] In such circumstances amphotericin B has been used intravenously or combined with the intraperitoneal route.[283] A peritoneal dialysate final concentration of amphotericin B of approximately 2–5 μg/ml will inhibit most Candida species; however, even this concentration of amphotericin may be prohibitively painful. Flucytosine and miconazole have also been used in the treatment of fungal peritonitis.[217] In general, it is useful to begin to treat these fungal infections by the oral route (e.g., flucytosine, ketoconazole) although combined systemic and intraperitoneal therapy may be required. Cases that remain resistant to therapy will probably require catheter removal.

The duration of antibiotic therapy is variable, and depends on the specific cause of peritonitis and host factors. The less immunocompromised the host, the shorter is the duration of therapy. In all instances, this should be at least a week. Since many patients are abnormal (nephrotic syndrome, cirrhosis, renal failure), at least 2 weeks of therapy is needed. Tuberculous peritonitis, of course, may require 9 months to a year of therapy with at least two first-line drugs (e.g., isoniazid and rifampin).

Prevention

Prevention may be useful in patients undergoing chronic ambulatory peritoneal dialysis. A recent study demonstrated that 1 g of cloxacillin given at bedtime reduced the frequency of staphylococcal infections in these patients.[129] Extension of these observations by other workers may suggest alternative chemoprophylactic regimens.

Complications

Complications of peritonitis can be seen in two stages. Initially, dehydration, septicemia, shock, and death may occur in acute bacterial sepsis and in peritonitis associated with bowel gangrene or perforation. Tuberculous peritonitis, if untreated, may also be fatal in as many as 50%

of cases. More frequently, however, peritonitis leads to the formation of intraperitoneal abscesses, particularly when *Staphylococcus aureus* or *Pseudomonas aeruginosa* are involved. Persistent fever and/or leukocytosis are warning signals that this complication may be developing.[218] Adhesions and intermittent abdominal pain syndromes are also seen. Rarely, hydronephrosis and hydroureter may occur in response to peritoneal irritation. The pathogenesis is thought to be similar to that responsible for paralytic ileus.[230] The long-term prognosis for patients with most forms of peritonitis is excellent, if abscesses are carefully drained and adequate antimicrobial therapy provided.

Appendicitis

Appendicitis is the most common abdominal condition requiring surgery in North America. The problem is one of obstruction with secondary infection, and the outcome depends on the speed of diagnosis. Patients with symptoms lasting longer than approximately 48 h are likely to have gangrenous changes of perforation, both of which are associated with increased morbidity and subsequent complications. The diagnosis is often difficult because of the many conditions that can be associated with acute abdominal pain and fever, and the nonspecific signs seen with appendicitis. The younger the patient, the more difficult is the diagnosis.

Etiology

Obstruction is usually secondary to unknown causes, although impaction of pinworms, fecal material, and foreign bodies has been described. Sometimes, extrinsic compression or bowel edema due to infection may predispose the patient to appendicitis.

Differential Diagnosis

It should be remembered that pneumonia may also cause fever and abdominal pain. Hence, a chest X-ray should routinely be obtained in patients with this presentation. Moreover, influenza B may present with severe abdominal pain, even in the absence of respiratory signs.[223] Gastrointestinal and lymphatic (mesenteric lymphadenitis) infections due to *Yersinia enterocolitica, Y. pseudotuberculosis,* and Campylobacter may also result in "pseudoappendicitis" syndromes, even in newborns with colic.[251] In fact, many of these patients have been operated on early in their course of disease before diarrhea became obvious. Urinary tract infection, pancreatitis, atypical measles, and, occasionally, enterovirus infections[223] may also mimic appendicitis. Add to these hepatitis, infectious mononucleosis, ovarian pathology, intussusception, volvulus, Meckel diverticulum, and school phobia, and one can easily understand the difficulty in making an early diagnosis in many patients.

Clinical Manifestations

In patients over the age of 2 years, abdominal pain, nausea, vomiting, and anorexia are the most consistent findings in acute appendicitis.[249] In those under 2 years, fever, vomiting, diarrhea, and abdominal distension are more prevalent. Leukocytosis with a shift to the left may be present, although this does not specifically indicate the diagnosis. Nor does the radiographic finding of ileus. Free air in the peritoneal cavity suggests perforation. Experience with radioisotope scanning is limited and, because of the time factor involved, may not be a useful approach.

The diagnosis of appendicitis in newborns is even more difficult and the mortality rate in infants may be 50% or greater.[357] Edema of the abdominal wall and abdominal distension are important signs, albeit late ones, in this age group.

Complications

The mortality rate in appendicitis in North America is approximately 0.2% overall, and 0.5% when gangrene is present. However, in children under the age of 8 years, mortality rates of 2–3% have been reported.[249] Wound infection, peritonitis, septicemia, bowel obstruction, and intraperitoneal abscesses in and around organs, such as the liver, are also seen.

Treatment/Prevention

Although acute appendicitis and its great imitator, mesenteric lymphadenitis, cannot be prevented, some of the complications of surgery in these patients can be. There is evidence that prophylactic administration of antibiotics is not very useful in acute appendicitis without gangrene or perforation.[299] However, perioperative prophylactic antibiotics are useful in patients with gangrene or impending or early perforation.[59] A combination of clindamycin plus gentamicin is useful in this situation.[161] When either peritonitis or abscess formation is not present at the time of the operation, antibiotics can be discontinued on the day of surgery (they are usually started approximately 1 h before operation).

When peritonitis is present, appropriate smears and cultures should be obtained and antibiotics continued for approximately 1 week. Antibiotics active against *Bacteroides fragilis* and *Pseudomonas aeruginosa* are important components of the medical management of perforated appendicitis.[161] Anaerobic cultures should be included and defervescence is expected within 48–72 h. Should discharge, fever, severe abdominal pain, ileus, etc., continue, attempts to diagnose intraperitoneal abscesses that may have been missed at operation, or that developed subsequently, should be made. When discovered, these should be surgically drained and treated with appropriate antibiotics. Removal of necrotic tissue, adequate drainage, and nutritional support are the mainstays of treatment of these patients.

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7

Skin Infections

Skin Infections

Nonspecific Rash and Systemic Infection

The causes of skin infections are extremely diverse. Moreover, the skin can also be involved in infections and illnesses affecting other organs in the body. Thus, nonspecific rashes may be seen with a wide variety of infections (Table 7–1). Macules are generally erythematous, although occasionally pigmented macules can be seen. The majority of macular erythematous, papular, and vesicular rashes are due to viruses, especially enteroviruses (Fig. 7–1). Although viruses are probably responsible for most petechial rashes, it is safer to presume treatable causes initially so that fulminant disease, such as meningococcemia and other septicemias, is not missed (Table 7–2).

In cases of nonspecific rashes (Table 7–1), it is useful to remember that the maculopapular and urticarial rashes, seen with hepatitis or Epstein-Barr virus infection, may reflect liver disease, even though the patient is not jaundiced. This has been called Gianotti disease (Chapter 6), and description of the liver component is important for both prognosis and prevention of spread.[274] Cytomegalovirus infection is sometimes associated with macules and petechiae in the newborn with congenital infection. This is also true of congenital rubella virus infection. Rubella, vaccinia and variola, are, it is hoped, included for historical interest, since these conditions are entirely preventable. Respiratory viruses, with the exception of adenovirus, are an uncommon cause of nonspecific skin rashes.

Clues to the cause of rash may reside in a specific noncutaneous manifestation, such as conjunctivitis (adenovirus or mycoplasma), gastroenteritis (Salmonella or Shigella), or jaundice (hepatitis B or leptospirosis). When petechiae are involved (Table 7–2), careful exclusion of systemic

TABLE 7-1. Infectious Causes of Nonspecific Rashes

Causative Agent	*Rash*
Viruses	
Adenovirus	Macules
Epstein-Barr virus	Macules, petechiae, urticaria
Cytomegalovirus	Macules, petechiae
Enteroviruses	Macules/papules, petechiae, vesicles
Alphaviruses	Macules, petechiae
Chikungunya	
O'nyong nyong	
Ross river	
West Nile	
Dengue	Macules, petechiae
Lassa fever	Macules, petechiae
Hepatitis B	Macules/papules, urticaria
Vaccinia	Papules/vesicles
Variola	Papules/vesicles
Bacteria	
Salmonella	Rose spots (macules)
Shigella	
Brucella	Macules
Bartonella	Macules
Rickettsia	
Typhus	Macules, petechiae
Rocky Mountain spotted fever	
Mycoplasma	Macules, papules, petechiae, vesicles, urticaria
Fungi	
Candida	Macules, papules, pustules
Coccidiomycosis	Macules
Protozoa	
Toxoplasmosis	Macules
Parasites	
Schistosoma	Macules, papules, urticaria
Amoeba	Ulcers

infections due to meningococcus, *Haemophilus influenzae,* and streptococci can be lifesaving.

Mycoplasma

Rashes associated with mycoplasma are particularly diverse. Not included in Table 7–1 is the fact that mycoplasma and some of the viral antigens can also be associated with severe hypersensitivity rashes, including Stevens-Johnson syndrome (Fig. 7–2). The pathogenesis of these hypersen-

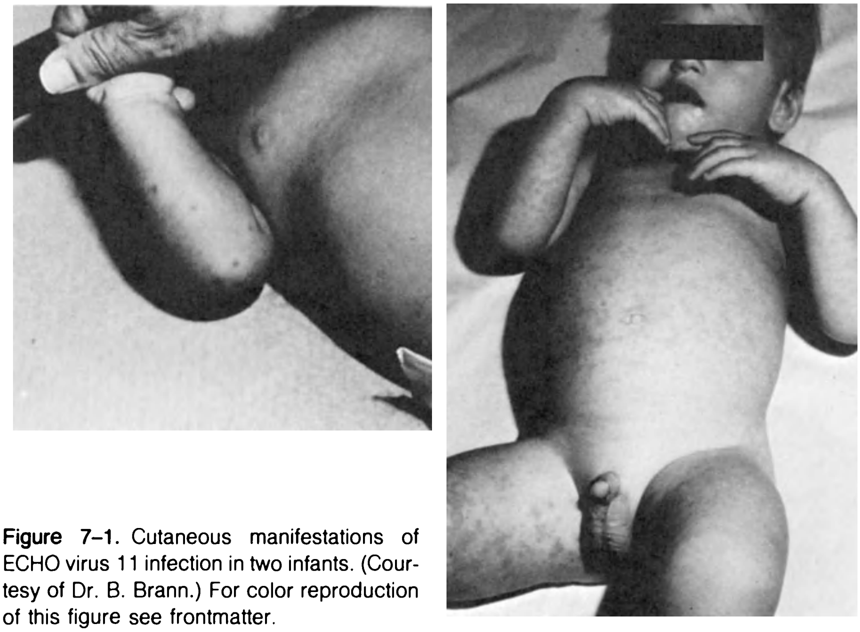


Figure 7–1. Cutaneous manifestations of ECHO virus 11 infection in two infants. (Courtesy of Dr. B. Brann.) For color reproduction of this figure see frontmatter.

sitivity reactions is unclear and it is often also possible to define drugs, patent medicines, and allergens to which these patients have been exposed. Nonetheless, the association of respiratory symptoms with erythema multiforme should suggest the diagnosis of mycoplasma infection. Elevated cold agglutinin levels may be present. Therapy for mycoplasma with erythromycin, or tetracycline in children over 8 years of age, for approximately a week may be helpful.

TABLE 7–2. Infections Associated with Petechiae

N. meningitidis
N. gonorrhoeae
H. influenzae
Streptococcus pyogenes
Streptococcus pneumoniae
Yersinia pestis
Enterovirus
Epstein-Barr virus
Cytomegalovirus
Rubella
Colorado tick fever
Arboviruses
Rickettsiae
Mycoplasmae
Rat-bite fever

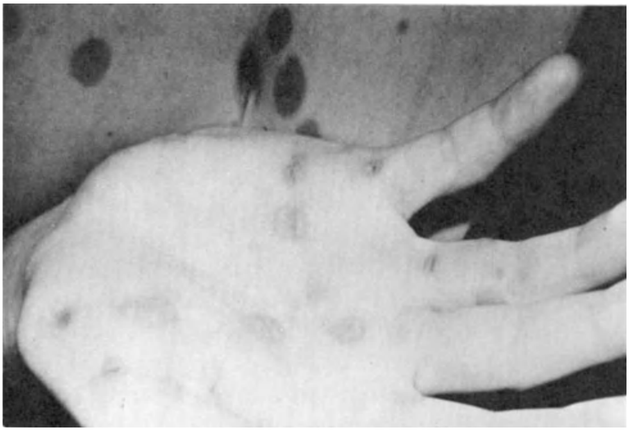


Figure 7–2. Erythema multiforme in a patient with *Mycoplasma pneumoniae* infection.

Rashes Involving the Palms and Soles

When an erythematous macular (and sometimes papular) rash involves the palms or soles, or both, specific diagnoses should be considered (Table 7–3). Historical features, such as administration of killed measles vaccine or medication, may uncover the cause. In certain geographical areas, the association of fever and maculopapular rashes involving the palms and soles may require therapy for Rocky Mountain spotted fever, pending exclusion of other causes of infection and further clinical developments. This may also be true for some petechial rashes. Extremely rarely, a history of rate bite within a week (*Streptobacillus moniliformis*) to 6 weeks (*Spirillum minus*) will point to the cause of intermittent fever, migratory sterile arthritis, and maculopapular or petechial rash including the palms and soles.[249]

TABLE 7–3. Rashes Involving the Palms and Soles

Rocky Mountain spotted fever
Coxsackieviruses
Drug hypersensitivity
Syphilis (secondary)
Atypical measles
Infectious mononucleosis (Epstein-Barr virus)
Mucocutaneous lymph node syndrome (Kawasaki disease)
Rat-bite fever
Streptococci
Leptospirosis

Specific Rashes

Sometimes the skin rash may have a more specific appearance, such as pustules with or without ulcers (Table 7–4). The vast majority of pustular lesions are due to *Staphylococcus aureus.* When the pustules are large and any confusion in the diagnosis exists, examination of the fluid by light microscopy and gram stain will usually define the cause. Of course, the presence of polymorphonuclear leukocytes and gram-positive cocci is not constant, even with staphylococcal infections. In appropriate hosts, such as leukemic patients, the presence of such lesions (ecthyma gangrenosum) should also suggest the possibility of gram-negative septicemia, especially due to *Pseudomonas aeruginosa.* Historical features, such as sexual contact with infected partners, may prompt a diagnosis of gonococcemia, whereas occupational exposure, such as taxidermy or animal skinning, may suggest diagnoses of anthrax or tularemia. Tularemia and rickettsial infections may also be associated with nodules or scars at the site of a tick bite, for example, in cases of scrub typhus (*Rickettsia tsutsugamushi*) and Rocky Mountain spotted fever (*R. rickettsii*). Other epidemiologic clues to causes can be defined for leishmaniasis (oriental ulcer), blastomycosis, and granuloma inguinale. Some arthropod bites may also leave ulcerated and pustular lesions. Superinfection with Staphylococcus and Streptococcus is most common in areas with warm climates and in populations with poor hygiene. Occasionally, outbreaks of folliculitis and pustulosis can be seen in subjects frequenting contaminated bathing facilities. In North America, this has recently been reported in members of a health spa in which inadequate chlorination led to contamination of the waters by *Pseudomonas aeruginosa.*[130] Ulcerative lesions may rarely be associated with gastrointestinal or visceral amebiasis.[256]

TABLE 7–4. Infectious Causes of Pustules/Ulcers

- *Staphylococcus aureus*
- *N. gonorrhoeae*
- *N. meningitidis*
- *B. anthracis* (anthrax)
- *Listeria monocytogenes*
- *F. tularensis* (tularemia)
- *H. ducreyi* (chancroid)
- Pseudomonas
  - *aeruginosa*
  - *pseudomallei* (glanders)
- Candida
- *Blastomyces dermatitidis*
- Leishmaniae
- *Entamoeba histolytica*
- Arthropod bites

Skin Infection Associated with Animal Contact

Specific animal contacts may also suggest the cause of skin infections (Table 7–5). Although many of these infections are rare in developed countries, they may be seen when susceptible hosts visit endemic regions or when exotic pets are taken into the home. Among these, tularemia, plague, and Marburg disease may be extremely virulent and life-threatening for man. Finally, pruritic linear cutaneous eruptions (Fig. 7–3) may suggest the presence of parasitic or arthropod infestations (Table 7–6). Some of the systemic infections in which the skin is the predominant organ of involvement, and infections limited to skin, are described in detail below.

Tick Bites

Tick bites usually go unnoticed until the tick is discovered, a papule or local infection occurs, or systemic consequences occur (Table 7–7). Rarely, bizarre cutaneous lesions, marked by blisters, pruritus, and fever are seen with tick bites in Middle Eastern countries.[141]

Viral and Presumably Viral Syndromes

Measles

Although global eradication of measles is considered achievable, infection due to this RNA myxovirus is still prevalent in many parts of the world.

TABLE 7–5. Infectious Causes of Skin Eruptions Associated with Animal Contact

Infection	*Animal Contact*	*Predominant Skin Lesions*
Monkeypox	Monkeys	Vesicles
Tanapox	Monkeys	Vesicles
Marburg disease	Monkeys	Macules/exfoliation
ORF	Sheep	Nodule
Paravaccinia (Milker's nodule)	Calves	Nodule
Foot and mouth disease	Cattle	Vesicles
Chlamydia psittaci	Birds	Macules/erythema
Spirillum minus	Rat	Macules/papules
Yersinia pestis (plague)	Rat	Petechiae
Leptospirosis	Rat/dog	Macules
Tularemia	Rodents/rabbits	Nodule/ulcer
Toxocariasis	Dog	Creeping eruption

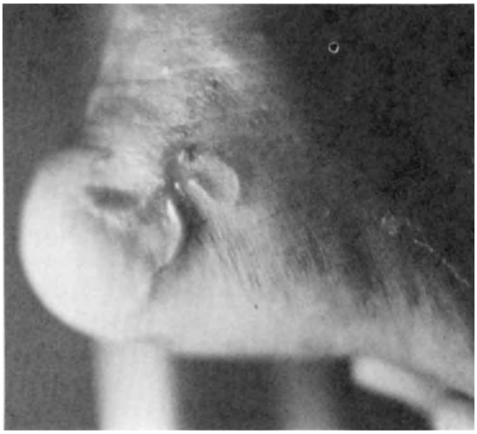


Figure 7–3. Cutaneous larva migrans (Toxocara).

Infections during pregnancy and the perinatal period are discussed in Chapter 3, and measles vaccination in Chapter 1.

Clinical Manifestations. Measles is among the most common contagious illnesses of children in areas where effective vaccination programs have not been implemented. In contrast, it is becoming rare for physicians to acquire experience with this condition in North America. The incubation period for measles is approximately 10 days (range 7–14). During this time, respiratory infection, primary viremia, and lymphatic infection take place. Both primary and secondary viremias are short-lived. Since primary viremia usually occurs within 3 days after respiratory infection, immune serum globulin is most effective in preventing illness when administered during this period of time. The disease is characterized by high fever, conjunctivitis, coryza, and bronchitis, which occur several days before the onset of the rash (Fig. 7–4). Mucosal lesions can be noted 1 or 2 days before the onset of the skin rash. These are referred to as Koplik spots when they are noted on the buccal or gingival mucosa.

Without a history of contact, the modern physician is often perplexed by the child with the aforementioned manifestations who appears to have symptoms of toxicity. Rather than ascribing them to the classic prodrome of measles, the physician should bear in mind that many other diagnoses are often suggested. For example, these children are often thought to

TABLE 7–6. Cutaneous Larva Migrans (Creeping Eruption)

Toxocara canis and *T. cati*
Strongyloides stercoralis
Ancylostoma braziliensis
Scabies (*Sarcoptes scabiei*)

TABLE 7-7. Tickborne Diseases

- Rickettsial
  - Typhus
  - Rocky Mountain spotted fever
  - Q fever
  - South African tick bite fever
- Viral
  - Colorado tick fever
  - Powassan virus encephalitis
- Bacterial
  - Tularemia
  - Relapsing fever
- Protozoan
  - Babesiosis
- Toxic
  - Tick paralysis

have otitis media, bronchitis, pneumonia, septicemia, mucocutaneous lymph node syndrome, etc., when they are seen before the onset of the rash. The temperature is often above 39°C, and cough is prominent. Infants and adults are particularly distressed by this infection and have higher complication rates. After 3–7 days of this illness, the red macular rash of measles usually begins on the face and progresses over the trunk

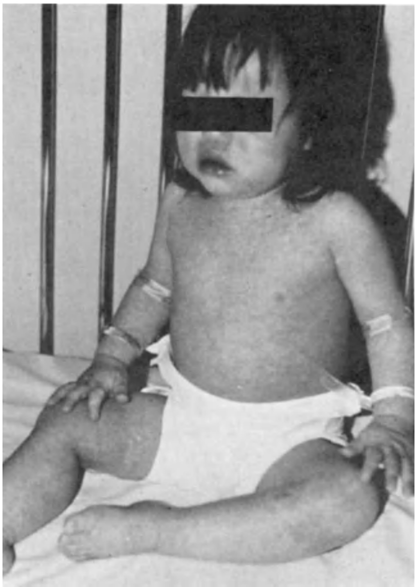


Figure 7–4. Measles.

and extremities during the subsequent 4–7 days. Classically, as the rash begins to involve the arms and legs, fever and toxicity become markedly reduced and recovery is imminent. The rash is sometimes followed by a fine desquamation.

Modified Measles. The clinical expression of measles infection can be diverse (Table 7–8). Classic measles is described above. In modified cases, passive immunization, acquired transplacentally from immune mothers, or by passive administration of immune globulin, may make the course milder and shorter.

Atypical Measles. Recipients of killed measles vaccine when exposed to natural infection may develop a syndrome known as atypical measles. This condition is characterized by rash and swelling of the extremities, including rash on the palms and soles (Fig. 7–5). Because of this, and the extreme toxicity seen in some of these patients, a diagnosis of Rocky Mountain spotted fever has occasionally been made in such patients. Other components of the atypical measles syndrome include pneumonitis, pleural effusion, and severe abdominal pain. The abdominal pain is probably related to pneumonia, but may also be due to involvement of lymph nodes and blood vessels. The pain can be so severe that in some instances patients have been subjected to exploratory laparotomy and appendectomy, on the suspicion that appendicitis was responsible. Occasionally, the rash may take on a vesicular appearance, which leads to confusion of this condition with varicella or coxsackie virus infection. A recent study of the immune response of these hosts indicates that atypical measles may represent an infection that is arrested at a different stage than natural infection and elicits both hypersensitivity and host immune responses to selected viral antigens.[9]

Diagnosis. The diagnosis of measles is usually made on clinical grounds and on the basis of exposure and immunization history. Although measles virus can be grown in tissue culture, this diagnostic method is rarely used. Serologic confirmation of the diagnosis is available by demonstra-

TABLE 7–8. Classification of Measles Infections

Classic Measles:	See text
Modified measles:	Classic course shortened and rendered mild by passive immunization with measles antibody
Atypical measles:	Generalized but atypical expression of measles infection in recipient of killed measles vaccine

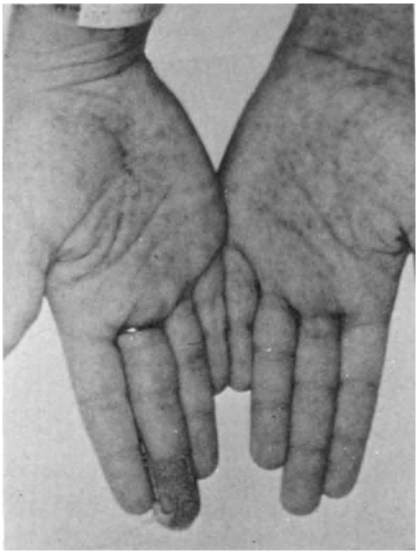


Figure 7–5. Atypical measles rash on palms. For color reproduction of this figure see frontmatter.

tion of a fourfold or greater rise in complement-fixation or hemagglutination-inhibition antibody titers.

Complications. Natural measles is a severe illness, particularly in young infants, adults, and immunocompromised hosts. In the last instance, fatal disease has been reported in children with nephrotic syndrome[210] or leukemia. This is more clearly understood when the pathogenesis of the disease is considered. Both humoral and cell-mediated immune responses are important.[115] Hence, patients who are severely malnourished,[325] those with underlying malignancies, and those with other causes of immunosuppression are at highest risk for invasive complications (Table 7–9). Gastrointestinal complications include acute and chronic diarrhea, ileocolitis, and appendicitis. Patients who are malnourished may be severely compromised by measles infection of the gastrointestinal tract.[17] Kwashiorkor may result in severe cases.

The most dreaded complications of measles are the development of giant cell pneumonia, which can be seen in adults[125] or in children with underlying malignancy,[338] encephalitis,[133] and other neurologic complications, including Guillain-Barré syndrome.[191] Attempts to modify measles encephalopathy by the use of interferon have been unsuccessful.[232] The incidence of encephalopathy, which can occasionally occur without a rash,[214] is approximately 1 of every 1000 reported cases of measles. Approximately 15–50% of these patients die or have permanent neurologic sequelae. The overall death rate in measles is also around 1/1000 cases. Other bacterial complications, such as otitis media and bronchitis, are common but readily treatable. Hepatic dysfunction[206] and acute

TABLE 7-9. Complications of Measles

- Early
  - Otitis media
  - Conjunctivitis
  - Keratitis[67]
  - Laryngitis
  - Laryngotracheobronchitis
  - Bronchitis
  - Bronchopneumonia
  - Pneumonia: giant cell ± superinfection
  - Enteropathy
  - Hepatitis
  - Neuropathy
  - Encephalitis
  - Mycocarditis
  - Pericarditis
  - Hemorrhagic measles
  - Reactivation of tuberculosis
  - Death
- Late
  - Bronchiectasis
  - Subacute sclerosing panencephalitis (SSPE)

glomerulonephritis[193] have also been reported, the latter due to glomerular immune complex deposition.

Subacute Sclerosing Panencephalitis. A late but rare (estimated to occur in fewer than 1 million infections) complication of natural measles is subacute sclerosing panencephalitis (SSPE), a condition in which mental deterioration, myoclonic seizures, and death may occur many years after natural measles.[218A] The risk appears higher for patients who had natural measles in the first year of life. Fortunately, this complication is less common after vaccination than after natural disease.[218] This manifestation of measles infection seems to represent a persistence of the virus in an incomplete form in brain tissue. The pathogenesis includes both persistent infection and host immune responses to the presence of the viral antigen.[71] The exact mechanism whereby this selects certain hosts is not understood. SSPE is often difficult to diagnose, since the clinical expression of this degenerative brain disease is extremely variable. This variability includes both the rate of onset (usually insidious) and expression of disease.[288] The latter may involve several aspects of behavioral, intellectual, and motor function, as well as visual and speech dysfunction. The electroencephalogram is markedly abnormal, with periodic suppression bursts. The only abnormality of the cerebrospinal fluid is an elevated protein (globulin) concentration, usually containing measles complement-fixation or hemagglutination-inhibition antibody.[284] In the absence of hemorrhage, this CSF antibody is rarely seen in any other condition except measles encephalitis and multiple sclerosis. Serum measles antibody titers are also very high in SSPE. There is no specific treatment, although preliminary attempts at therapy with antiviral drugs and immunostimulators have been reported.[158]

Prevention of Measles. Use of measles vaccine is discussed in Chapter 1. This disease is spread through respiratory secretion droplets, or through direct contact with nasal or throat secretions of infected persons; it is possible that airborne transmission and fomites may also be responsible. Most susceptible exposed individuals will develop infection. This stresses the importance of strict isolation procedures for patients with measles when they are hospitalized or discovered in closed populations. All exposed, susceptible contacts should be given vaccine to prevent infection, if the contact is discovered within 48 h of exposure. If the exposure time is longer or uncertain, as often occurs in household contacts, or if vaccine is contraindicated, immune serum globulin should be given. In appropriate subjects, this is followed by measles vaccination approximately 3 months later. The disease is communicable from approximately 1 to 2 days before the prodrome to 4 or 5 days after the appearance of the rash.

The prospect of eradicating measles worldwide is real.[143] Measles has an enormous impact on health, since it is estimated that it is still one of the leading causes of death in children in the first 5 years of life in many developing countries. The deleterious effect of measles on children with malnutrition and diarrhea syndromes is severe and often life-threatening. The morbidity associated with measles in all populations, including otitis media, pneumonia, encephalitis, and neuropathy is also great. Since the vaccine is associated with a low incidence of side effects and provides long-lasting immunity, the major obstacles to global eradication of this disease are resources for surveillance and vaccine delivery.

Varicella

Chickenpox (varicella) is still a common childhood infection. In normal hosts, it is benign and self-limited, but in certain situations, it can be life-threatening. Features of this infection in pregnancy and in the newborn period are discussed in Chapter 3.

Epidemiology/Pathogenesis. Chickenpox is seen in approximately 90/100,000 individuals/year in the United States. Sixty percent of cases occur in children between 5 and 9 years of age, and 80% in children under 10 years.[247] Although chickenpox is benign in most situations, death occurs in as many as 7/10,000 reported cases. The risks of complications and mortality are increased in subjects under 5 and over 20 years of age, and in immunocompromised patients.[219] Visceral involvement has been noted in approximately one-third of children receiving chemotherapy for cancer, and death in 7%.[98]

Chickenpox is most commonly seen in winter and spring and can be spread by either direct contact or through aerosol droplets.[131] There are two brief cell-associated viremic periods in normal hosts,[126] and a more prolonged viremia in progressive varicella in immunocompromised patients.[225]

Clinical Manifestations. After an incubation period of 10–21 days (average 14 days), the disease begins with a mild prodrome consisting of low-grade fever and malaise. In many children, there is no prodrome. The first indication of chickenpox is often the appearance of a small "dew drop" lesion on the trunk or face and/or crops of small macules or papules in the same area. Lesions then appear on the extremities and progress from macules to papules, vesicles, pustules, and scabs (Fig. 7–6). Extreme pruritus is common and lesions may be present on the mucous membranes and conjunctiva as well. There is generally only mild fever and moderate malaise.

There are all degrees of cutaneous involvement in chickenpox, from only a few lesions to large crops covering the entire body. The lesions are full of virus and highly infectious. Careful hygienic practices are necessary to avoid autoinoculation, spread to contacts, and staphylococcal and streptococcal skin superinfections. Virus may be spread (possibly from the respiratory mucosa) for 1–2 days before the onset of the rash, and from skin and respiratory sites during the period when active skin lesions (i.e., before crusting of all lesions and cessation of appearance of new crops) are present. The total duration of illness is generally 5–7 days.

Progressive varicella is characterized by continuing eruption of lesions and high fever beyond the first week of illness. It has been described in normal hosts, those receiving corticosteroids, and in immunocompromised patients. Abdominal pain, jaundice, and the inappropriate antidiuretic hormone syndrome are suggestive of progressive disease and visceral involvement in such patients.[219]

Diagnosis. Chickenpox is one of the most highly contagious illnesses. Over 90% of susceptible contacts develop infection after exposure; hence the diagnosis is often facilitated by epidemiologic history. Moreover, vesicular lesions are fairly distinct and suggest a limited differential diagnosis including infections with *Mycoplasma pneumoniae*,[185] coxsackievirus, smallpox, and monkeypox.[224] Occasionally, however, it is important to ascertain the diagnosis of chickenpox more exactly. This is particularly

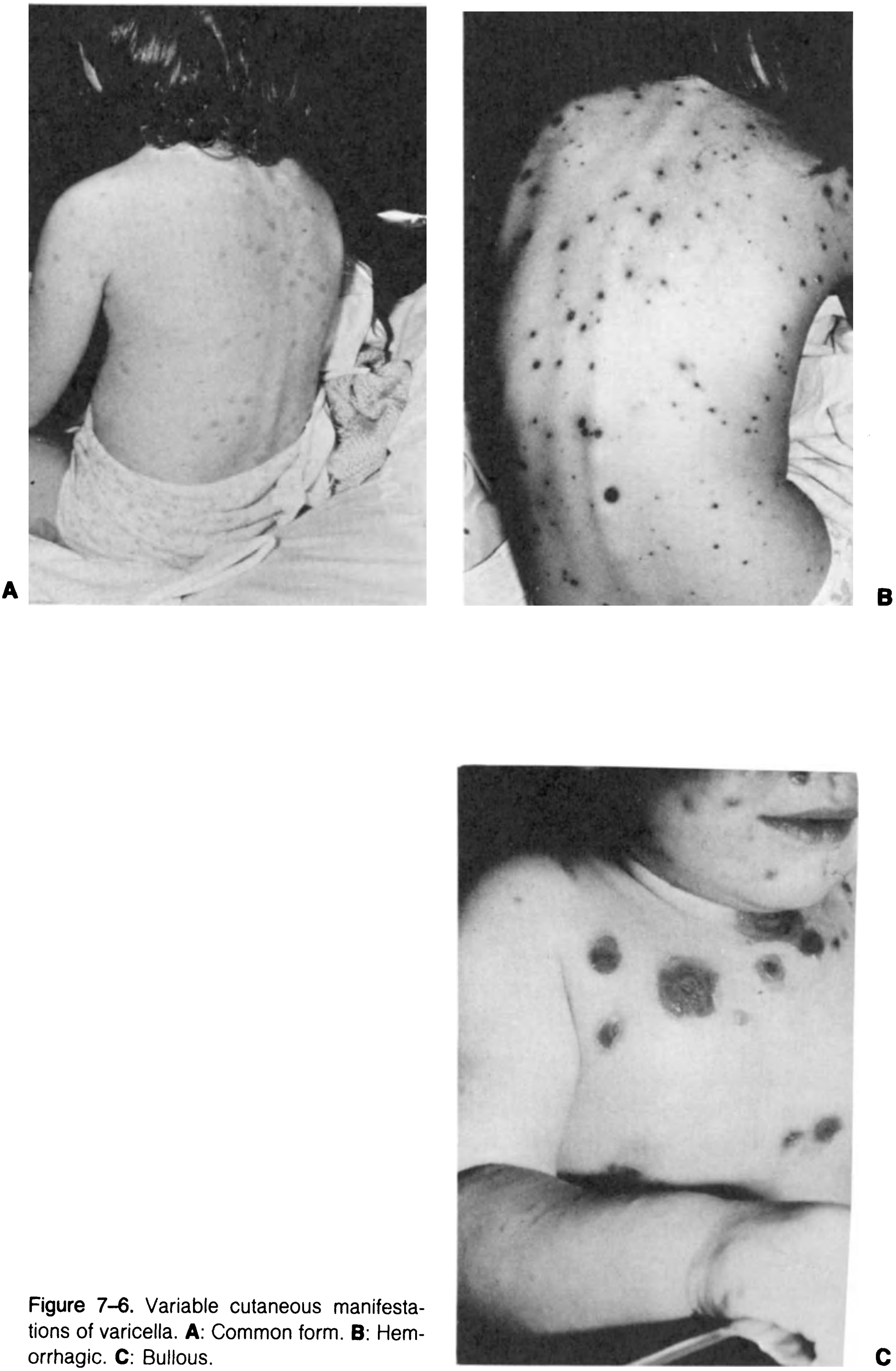


Figure 7–6. Variable cutaneous manifestations of varicella. **A**: Common form. **B**: Hemorrhagic. **C**: Bullous.

true in immunocompromised patients, or their contacts, for whom specific antiviral therapy is required. In such situations, a Tzanck smear of cells scraped from the lesion base will show multinucleated giant cells. Virus also can be identified rapidly in vesicular lesions by means of electron microscopy, or antigen can be detected by counterimmunoelectrophoresis.[113] Although slower and more difficult, culture of the virus from these lesions can be performed in tissue culture as well.

When the question of immunity in a contact of a patient with varicella arises, the FAMA, ELISA, or the anticomplement-fluorescent antibody tests are most useful.[285] Complement-fixation antibody titers will be undetectable in approximately one-half of patients who had chickenpox several years prior to testing. Susceptibility can also be predicted by an investigational skin test.[299]

Treatment. In most cases, the only treatments required are hygienic and antipruritic. Gentle bathing with a hexachlorophene soap may help prevent staphylococcal superinfection of the skin lesions, particularly in patients with widespread lesions. Cool baths and application of calamine, or other topical antipruritic, may decrease itching. In extreme cases, a systemic antipruritic/antihistamine preparation may be useful, since some degree of sedation may be desired. Patients with varicella should avoid using aspirin, because Reye syndrome has been associated with both use of salicylates[319] and varicella.[148]

Patients with progressive varicella and those with extracutaneous complications (Table 7–10) may require specific therapy. Both vidarabine[326] and acyclovir[248] are active against varicella. These drugs should be administered systemically and for at least a 7–10-day period. Interferon also has a therapeutic effect against varicella in immunocompromised patients.[13] These patients should be under careful observation for progression of lesions, drug toxicities, and complications requiring other therapies.

Prevention. Although early vaccine studies showed promise, recent experience has indicated some loss of humoral immunity in immunocompromised children within 6 months to 2 years.[10] The prospects of a commercially available varicella vaccine for widespread application to normal subjects are still uncertain; however, immunity has persisted for 5 years in that population in Japan.[14] In the meantime, it is useful to prevent varicella in contacts at high risk for complications and progressive disease. This includes adults, newborn infants (if their mothers are susceptible), and immunocompromised patients. Patients with leukemia and those with renal transplants also are at particularly high risk.[97] In these cases, varicella zoster immune globulin should be administered, preferably within 72 h of exposure to varicella.[340] This material is commercially

TABLE 7-10. Complications of Varicella

- Acute
  - Progressive varicella
  - Disseminated varicella
  - Bullous varicella
  - Pneumonia
  - Death
  - Bacterial superinfection
    - *S. aureus*
    - Group A Streptococcus[293]
  - Hepatitis[94]
  - Reye syndrome[148]
  - Arthritis[25,336]
  - Disseminated intravascular coagulopathy[226]
  - Hemorrhagic varicella
  - Thrombocytopenia[334]
  - Keratitis[313]
  - Nephritis[290]
- Postinfectious
  - Cerebellitis
  - Encephalitis
  - Transverse myelitis[205]
  - Optic neuritis[58]
  - Zoster (shingles)

available and is administered as an intramuscular injection according to an age-adjusted dosage schedule (Chapter 1).

It should be remembered that immunity to varicella may be incomplete, particularly in patients receiving intensive cytotoxic and immunosuppressive therapy, and in those who are also treated with antiviral chemotherapy.[315] Clinical varicella in infants with preexisting humoral immunity has also been noted in a semiclosed domiciliary institution.[19] It is possible that exposure to virus is extensive and prolonged in these circumstances, and mild varicella may result when low levels of preexisting immunity are present. When patients need to be admitted to hospital for the treatment of chickenpox or its complications, the high degree of contagiousness of this disease should be kept in mind. Hence, careful handwashing and availability of rooms with negative-pressure ventilation are mandatory.[131] For those who are susceptible to chickenpox, it is best to avoid patient contact completely. If this is not possible, strict isolation technique (wearing gowns, masks, gloves; washing hands) should be used.

Prognosis/Complications. In general, the outcome of varicella is good. Some patients, however, develop acute complications that may be localized, such as staphylococcal superinfection or streptococcal cellulitis, or generalized, such as thrombocytopenia and various forms of coagulopathy (Table 7-10). Bullous skin lesions usually indicate the presence of staphylococcal infection (Fig. 7-6). Local pain may herald the onset of these lesions.[44] The most life-threatening complications of this disease are Reye syndrome, encephalitis, and pneumonia.[101] The last is seen with increased frequency in adulthood. After recovery from varicella, patients may develop localized cutaneous eruptions (herpes zoster—"shingles") confined to the dermatome served by specific sensory nerves, after reactivation of varicella virus in those neurons (Fig. 7–7). If the patient is immunosuppressed, such as those with Hodgkin disease, there is a chance that this reactivation may also lead to systemic disease with severe morbidity and occasionally mortality.[291] Hence, such patients should be treated with antiviral chemotherapy, as outlined above.

Herpes Zoster

Pathogenesis. Herpes zoster (commonly called "shingles") can be considered the reactivation form of varicella. In the vast majority of cases, this reactivation is localized to a specific dermatome. The localized nature of the eruption is due to the fact that the virus is latent in the ganglion cells of the neuron serving that particular dermatome. For unknown reasons, reactivation occurs and the virus is expressed at the skin surface in the form of papules and vesicles. This is apparently not related to a decrease in the amount of humoral antibody, but may involve alterations in cell-mediated immunity.[118] The increased incidence of reactivation in immunocompromised patients supports this theory.

For most purposes, herpes zoster can be considered similar to chickenpox when it extends beyond the dermatome and invades extracutaneous tissues. Hence, discussions of the clinical expression and treatment of varicella are relevant to this condition as well. The viruses are the same.

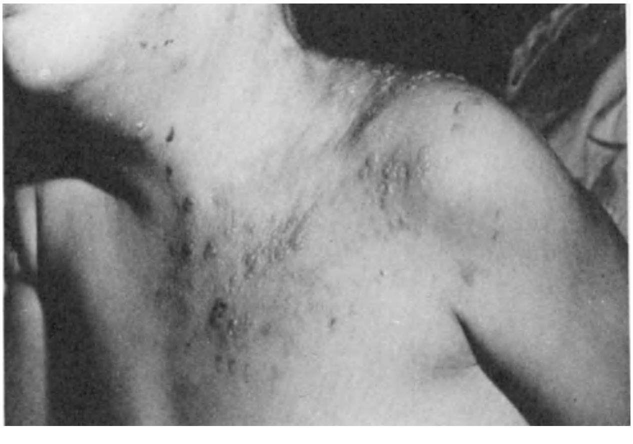


Figure 7–7. Herpes zoster.

Clinical Manifestations. The patient often experiences tingling, paresthesia, or pain at the site of the eruption (usually one to three sensory dermatomes) for several hours or days before erythema, followed by the appearance of papules and vesicles (and pustules) (Fig. 7–7). The degree of pain and distress is much milder in childhood than it is in the elderly, and systemic signs are rare. However, morbidity may be severe when dermatomes innervated by cranial nerves are involved. The total duration of vesiculation and scabbing is rarely more than 10 days, although in some patients lesions persist for several weeks. Regional lymphadenopathy is common. Occasionally, viruses other than varicella, such as herpes simplex[109] and echovirus 6,[209] may mimic this condition.

Rarely, extracutaneous involvement in herpes zoster includes the meninges[254] or deep viscera, such as the bladder and anus[156] or even the stomach.[329]

Diagnosis. The diagnosis of herpes zoster can usually be made by examination and history. A Tzanck (1% toluidine blue 0) smear of tissue from the base of the lesions will show intranuclear inclusion bodies. Virus can also be cultured and visualized by electron microscopy from these lesions. Demonstration of the presence of humoral antibody to varicella, at the onset of zoster, suggests this diagnosis, as does an anamnestic response later in the course. In almost all cases, except in severely immunocompromised patients, a varicella skin test would be expected to be positive in the early stages of zoster as well.

Treatment. The literature is replete with anecdotal accounts of medications that alleviate the acute distress and postherpetic neuralgias that occur with herpes zoster. Since the clinical manifestations are extremely variable, and the condition self-limited, these reports are difficult to interpret. Most recently, levodopa has been reported to decrease postherpetic neuralgia.[170] It should be remembered that postherpetic neuralgia is predominantly a manifestation of herpes zoster in the elderly patient.

Treatment of herpes zoster in normal infants and children is usually not necessary, except for mild analgesic and antipruritic topical medications. In immunocompromised patients, however, the risk of dissemination to other dermatomes and deep tissues increases. Some cases may be fatal. Hence, recent descriptions of the utility of antiviral chemotherapy are most welcome. Vidarabine[327] or acyclovir[21] can be used for treatment of acute herpes zoster in immunosuppressed patients, although, as stated above, this is rarely required in normal children. If preliminary results are confirmed, oral acyclovir may be relatively nontoxic and tolerated well, so that it could be used in normal patients as well. Patients undergoing bone marrow transplantation or other immunosuppressive procedures should certainly be treated with acyclovir, if herpes zoster develops.[283] Human leukocyte interferon is also useful in shortening the course of illness in such patients,[213] and both modalities may be combined in serious progressive infections in severely immunocompromised and malnourished hosts. Passive immunization with zoster immune globulin, or normal serum globulin, does not prevent dissemination in such hosts.[302] Systemic corticosteroids may slow healing and are of unproved usefulness.[328]

The lesions of herpes zoster contain virus, and appropriate isolation techniques (washing hands, wearing gowns) are needed to prevent spread to susceptible contacts who may develop varicella.

Prognosis. The vast majority of patients with herpes zoster do well, although several recurrences and scarring may be seen. Bacterial infection of the lesions of herpes zoster is unusual; however, a case of zoster complicated by staphylococcal toxic shock syndrome was recently reported.[154] Does the finding of herpes zoster in a normal individual warrant extensive examination for underlying cancer or other immunosuppressive disease? This question has often been asked, because of the association of herpes zoster with underlying malignancies. A recent study found that the relative risk of such patients developing cancer, or having an occult neoplasm, is actually low.[250] Hence, careful history and physical examination should suffice in the vast majority of patients who develop herpes zoster and are otherwise normal.

Rubella

Rubella can be prevented effectively by vaccination (Chapter 1). Natural infection occurs approximately 2½ weeks after exposure. Initial nasopharyngeal colonization is later followed by systemic spread of the virus. There is presumed to be a viremic phase, and virus has been isolated from the skin lesions, lymphocytes, and, occasionally, joint fluid.[138] The disease is usually mild, with low-grade fever and a diffuse maculopapular rash, less florid than in scarlet fever and less confluent and widespread than measles. Postauricular, suboccipital, or posterior cervical lymphadenopathy is common. Rubella arthritis is seen predominantly in adolescent and adult females. Rare complications include acute rubella encephalitis,[265] thrombocytopenic purpura,[236] and progressive rubella panencephalitis, a syndrome similar to measles subacute sclerosing panencephalitis, which can occur years after congenital or acquired rubella.[1]

Hand, Foot, and Mouth Disease

Epidemiology/Etiology. A papular, vesicular eruption on the hands and feet, associated with mouth lesions, is commonly seen in the summer and fall months among infants and children under 5 years of age. This is most frequently due to coxsackieviruses A16, A5, and A10, although outbreaks due to serotype A9[147] and enterovirus 71[149] have also been reported. These enteroviruses are widespread in the community at the time, and manifest differently in individual patients. The dermatotropism of these viruses is matched in some instances by their neurotropism, since some of these children have associated aseptic meningitis. This has been noted with particular frequency with enterovirus 71 in two Japanese outbreaks, in which 8–24% of children with hand, foot, and mouth disease had associated neurologic signs.[149]

Clinical Manifestations. After an incubation period of approximately 3–6 days, mild fever, sore throat or sore mouth, and decreased appetite are first noted. This is rapidly followed by the appearance of papules or vesicles, or both, on the hands and feet, including the palms and soles (Fig. 7–8). Lesions are also seen on the trunk, thighs, and buttocks of young infants, in whom macular and erythematous components may be more pronounced.[309] The mouth lesions resemble aphthae and are seen on the tongue and other mucosal surfaces. Symptomatic children are predominantly under 5 years of age, although older individuals may also be affected.

Fever is generally mild, sometimes absent, and may be accompanied by headache, mild vomiting or diarrhea, irritability, and, occasionally, signs of cerebellar or meningeal involvement. Lesions may be scant, suggesting herpangina or localized herpes simplex in some patients. Often, there are several hundred lesions and the disease may resemble chickenpox, atypical measles, Rocky Mountain spotted fever, or mucocutaneous lymph node syndrome. Although anorexia and pain may be present, the hand, foot, and mouth syndrome is generally mild and self-

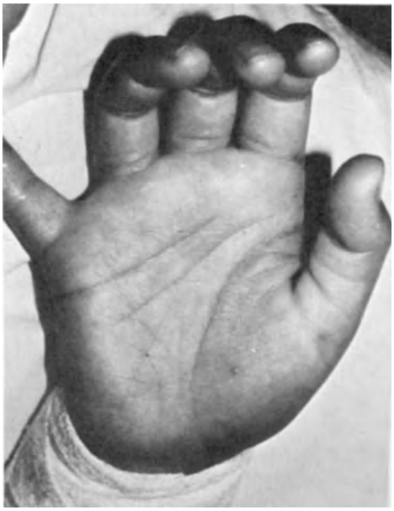


Figure 7–8. Palmar papulovesicles in patient with hand, foot, and mouth syndrome.

limited within 5–7 days. Rare complications include generalized skin involvement in patients with eczema[227] and severe central nervous system involvement.

Diagnosis. The hand, foot, and mouth syndrome is usually diagnosed on the basis of clinical and epidemiologic criteria, including the season (summer), familial nature of the outbreak, and the classic distribution of the lesions. Virus is present in these lesions and can be grown in tissue culture, but this is rarely necessary. Serologic confirmation can be made; however, this requires demonstration of type-specific neutralizing antibody and is not a very practical clinical approach.

Management. It is important to realize that coxsackieviruses are present in the lesions, but may also be present in the throat for 15 days, and in the feces for up to a month. Contagiousness is fairly high, with more than half of family members at all age groups acquiring the virus, although disease is manifest most frequently in preschoolers. Nosocomial outbreaks have been described in hospital populations,[220] reminding us that isolation techniques, including washing hands and wearing gowns, are recommended. There is no specific therapy and in the vast majority of patients the illness is resolved without any medication other than mild analgesics or antipyretics.

Herpes Simplex Infections of the Skin

Pathogenesis. Skin lesions are probably the most common expressions of herpes virus infection in man. It is estimated that as many as half the American population have had one or more episodes of herpes labialis or skin infection at some time in their lives. These infections are usually short-lived and benign; however, they recur in many individuals. Stimuli for reactivation are poorly understood and include exposure to sun, emotional and physical stress, menstruation, trauma, surgical denervation, and tooth extraction.[233] Recurrences are not related to changes in humoral immunity,[341] but may reflect altered T lymphocyte control. Localized skin herpes is rarely a problem, unless the host is immunosuppressed. In such patients, both primary and reactivation lesions may become chronic and last for several months, with necrosis and disfiguring effects.[287] In others, extracutaneous dissemination with severe consequences can occur.

Occasionally, normal hosts with altered local anatomic defences (and perhaps other immune dysfunction) can also become severely superinfected with herpes simplex virus. Examples include patients with burns, eczema,[48] and even staphylococcal impetigo.[134] Fatal, disseminated infection can even occur.[16]

Clinical Manifestations (Fig. 7–9). Herpes labialis is most common. Herpes paronychia and localized dermatitis are also frequently seen. Herpetic whitlow occurs in children with oral herpes and in adolescents with genital lesions.[96] Genital lesions are discussed in Chapter 10 and lesions affecting newborns in Chapter 3. Knowledge of the natural course of herpes labialis is important in counseling patients about contagiousness and clinical effects, and in interpreting the results of various therapies.[296] Pain or paraesthesia is often the first signs of herpes labialis and can be noted for the first 1 or 2 days, along with erythematous or papular skin lesions. This is quickly followed by vesiculation and swelling, which can last anywhere from 2 to 3 days. The lesions generally crust and heal during the subsequent 3 days, the total duration usually lasting between 6 and 8 days. Underlying conditions should be considered in patients with lesions that are progressive, or present for longer than 2 weeks.

Other skin manifestations of herpes simplex infection include varicella-like lesions, usually in immunocompromised patients,[195] and erythema multiforme.[89]

Diagnosis. The diagnosis of herpes simplex is usually made on the basis of the clinical appearance of the lesions of acute or recurrent herpes labialis or dermatitis. It is worthwhile to confirm the diagnosis virologically at some point, particularly in patients with underlying diseases. This can be done by viral culture, which is usually positive within 24–72 h. More rapid means of diagnosis currently include electron microscopic visualization of viral particles in vesicular fluid, fluorescent-antibody staining of cells from vesicles (Fig. 7–10) or, less specifically, visualization of giant cells or intranuclear inclusions in cells scraped from the bases of such lesions (Fig. 7–11). Direct methods of identifying virus antigen in vesicular fluid and other body sites are being developed and should facilitate rapid and inexpensive approaches to the diagnosis in the near future.

Treatment. Widely available diagnostic techniques are essential to the application of antiviral chemotherapy for herpes infections. Topical application of 5% acyclovir cream early in the course has been shown to reduce virus excretion and shorten the course in patients with herpes labialis.[102] In a similar trial, vidarabine affected neither viral excretion nor clinical outcome.[295] Use of acyclovir is probably most important in patients with primary infection and in those with underlying illnesses that may prolong the herpes simplex infection or lead to dissemination.[305] Included in the latter should be patients with eczema, who may have severe herpetic infection. It should be remembered that widespread and repeated use of acyclovir has the potential to select viruses resistant to

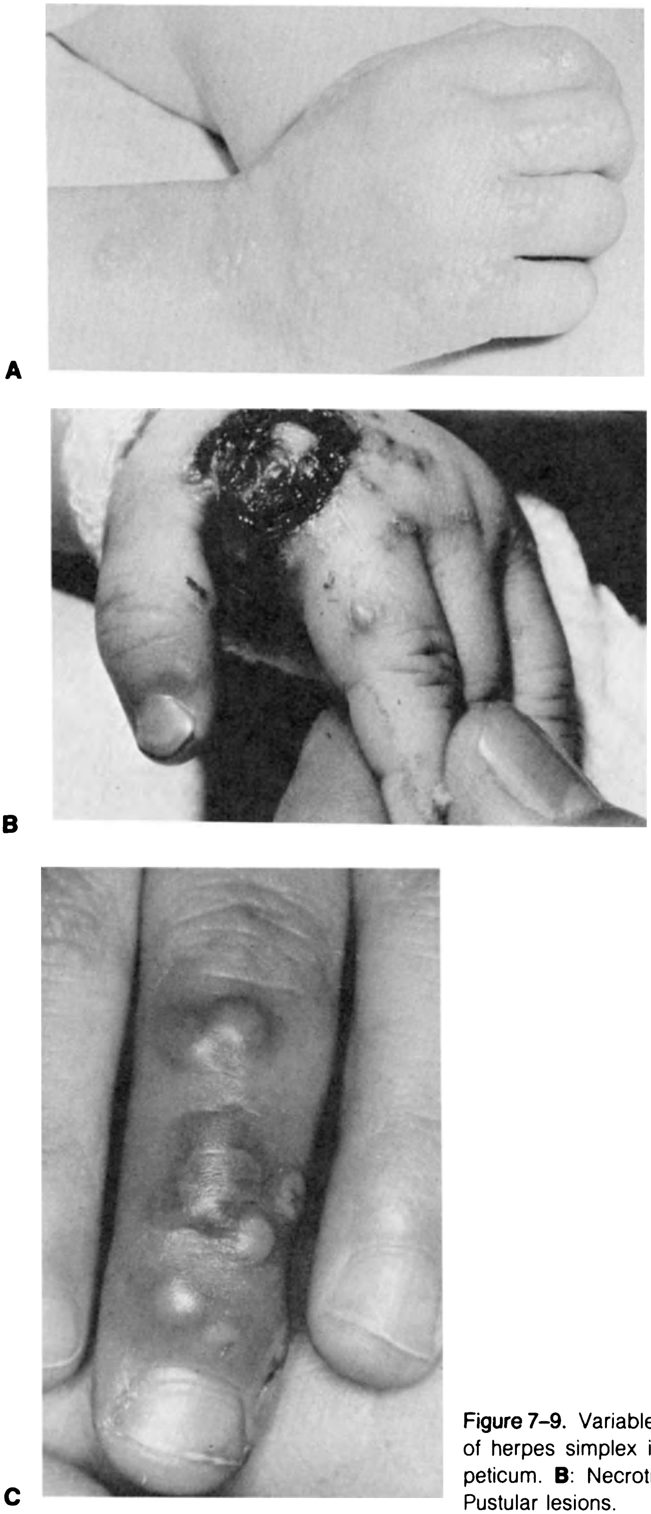


Figure 7–9. Variable cutaneous manifestations of herpes simplex infection. **A**: Eczema herpeticum. **B**: Necrotizing wound infection. **C**: Pustular lesions.

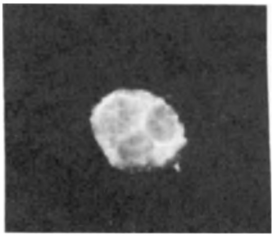


Figure 7–10. Demonstration of herpes simplex virus antigen in cell from the base of a vesicle. Direct fluorescence antibody technique. (Courtesy of Dr. J. Waner.)

the drug by means of synthetic pathways that avoid the need for thymidine kinase, the target enzyme for its antiviral action.[62]

The literature is replete with other therapeutic approaches claiming to be effective in the treatment of cutaneous herpes simplex infections. These reports should be looked at with skepticism, considering the extreme variability of clinical expression of this condition. When subjected to controlled study, several of these have been shown to be useless. These include ether,[129] lysine,[215] and smallpox vaccine.[216] The use of the latter is particularly deplorable, since morbidity, and even mortality, from smallpox vaccine have been reported in such patients.

Prognosis/Isolation. In general, herpes simplex skin infections, although ubiquitous, are benign and self-limited. However, recurrences in and around the eye, mouth, and genital region may be extremely distressing. Other problems arise when these infections are first encountered in immunocompromised patients or in those who are severely malnourished. In such patients, chronic and progressive disease, often with dissemi-

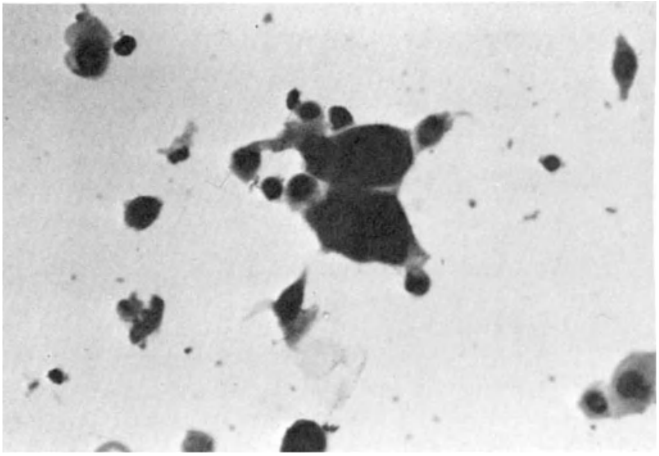


Figure 7–11. Positive Tzanck preparation from a patient with herpes simplex dermatitis. (Courtesy of Dr. G. Altshuler.)

nation, is possible. In such situations, mortality rates may be high, although chemotherapy with systemic acyclovir has markedly improved the outcome in these patients.

The threat of spread of infection to contacts is real, since vesicular and crusting lesions contain virus, as do oral secretions and hands. Viruses can survive up to 2 h on skin, 3 h on cloth, and 4 h on plastic.[312] Herpes is usually transmitted by direct contact, suggesting that handwashing and avoiding contact with patients at high risk are adequate isolation techniques.

Warts

Epidemiology/Etiology. Warts are benign epidermal neoplasms caused by human papilloma viruses. These DNA viruses comprise several antigenic types with some common features. They characteristically cause proliferation of epidermal cells with vacuolization and accumulation of superficial epithelial cells. Inflammatory reaction is minimal until spontaneous resolution begins to occur. The lesions often occur at sites of trauma and are most frequently seen on fingers, feet, and the perineal region. There is suggestive epidemiologic evidence that warts can be spread through sexual contact,[234] and it is also probable that laryngeal papillomas of infancy are related to genital warts in pregnant women.[179] The association is strong enough for some authorities to suggest cesarean section to prevent this occurrence when warts are present in the third trimester of pregnancy. Lesions are often more frequent, widespread, and difficult to treat in immunosuppressed patients[157] and in those with immunodeficiency diseases.[23]

Clinical Manifestations. Warts may be present on any skin or mucosal surface. Many terms in both English and Latin are used to describe them (Table 7–11). These classifications usually depend on the site and/or gross appearance of the lesions. Inoculation studies have demonstrated

TABLE 7–11. Classification of Warts

- Common wart (verruca vulgaris)
- Flat wart (verruca plana)
- Papilloma
  - Cutaneous
  - Mucosal, including laryngeal
- Periungual
- Plantar (mosaic)
- Condyloma acuminata
- Penile
- Digitate

an incubation period of approximately 3 months, although this is quite variable depending on the amount of virus, the site of infection, and the immunologic status of the host. Although these lesions are benign according to histopathologic criteria, considerable morbidity is often associated with them in terms of cosmetic effects. Moreover, respiratory obstruction may be a primary and life-threatening manifestation of laryngeal papillomatosis in young infants. Perianal, urethral, and genital warts may cause a variety of distressing signs and symptoms. When these are noted in prepubescent children, the possibility of sexual abuse should be considered.[69]

Diagnosis. The diagnosis is usually made by gross inspection, although the virus can be demonstrated in tissue preparations by electron microscopy, in frozen tissue by fluorescent antibody techniques, and in formalin-fixed tissue by the immunoperoxidase technique.[8]

Treatment. Warts disappear spontaneously in most hosts. The more immunocompetent the host, the more likely this will take place. However, in the best of circumstances, only 20–30% of warts spontaneously regress within a 6-month period and 50% within a year.[46] The problem with waiting for spontaneous regression, an event usually associated with host immune responses (antibody and probably cell-mediated immunity) to the viral antigen, is that new lesions may appear at different sites in the body during this time, and spread to contacts may also occur. As expected, a benign condition with a variable period of spontaneous regression is associated with many anecdotal reports of successful treatment modalities. Another factor that contributes to the confusion is the beneficial effect of nonspecific inflammatory treatments, via the liberation of viral antigen and the stimulation of appropriate host responses that contribute to their resolution. Thus, levamisole, transfer factor, smallpox vaccine, and a variety of superficial abrasives have been used. It should be remembered that spontaneously regressing warts, despite a gross clinical appearance, usually will not leave a scar. Hence, treatments should also be relatively benign and nonscarring.[252]

Topical liquid nitrogen applied weekly will form small blisters, and will be beneficial in the treatment of many common warts without leaving scars.[171] Podophyllin resin is often used for anogenital warts—25% in compound tincture of benzoin is applied weekly.[253] It is necessary to apply these treatments for 2–3 months in most cases. Recent experience with 5-fluorouracil and adenine arabinoside suggests that topical antiviral applications may also be useful.[84] Acyclovir occlusive dressing may also be beneficial, as may interferon, although controlled studies are lacking.[27] A last resort recommended for widespread and resistant warts is the use of autogenous vaccine, prepared from wart tissue from which viral antigens have been extracted, purified, and inactivated.[171] Surgery can also be used for digitate warts and for removal of laryngeal[282] and genital warts that cause obstructive symptoms. This has been made simpler and more efficient by development of the carbon dioxide laser.[99] It is worthwhile reiterating the long-term benign nature of warts and the importance of avoiding scarring, and potentially dangerous therapy (such as smallpox vaccine) for their treatment.

Prevention. Although not highly contagious, human papilloma viruses are spread by direct contact, particularly in moist areas that are frequently traumatized. Thus, some discretion in sexual contact for patients with these lesions seem judicious. Similarly, advice regarding cesarean section in mothers with prominent genital warts present at the time of delivery seems worthwhile.[84] Dermatologists' experience with this condition can be helpful in managing lesions that require surgery and topical liquid nitrogen treatments.

Molluscum Contagiosum

Another wart-like condition, molluscum contagiosum, is due to a pox virus that preferentially infects human epidermal cells. The disease is spread by direct contact with lesion material and is most commonly seen in young infants and sexually active individuals. Venereal transmission is often responsible for lesions that are noted in the perineal and lower trunk region.[196] Occasionally, these lesions can occur in immunosuppressed hosts, emphasizing the balance that normally exists between host immunity and localization of pox viruses.[266]

Clinical Manifestations. After an incubation period that varies from 1 to 8 weeks, multiple, pinhead-sized lesions appear in clusters on the trunk, face, extremities, or perineal region (Fig. 7–12). These gradually enlarge to approximately 1 cm; however, "giant" molluscum may be 2–3 cm in size. Occasionally, these lesions are pedunculated. A molluscum lesion

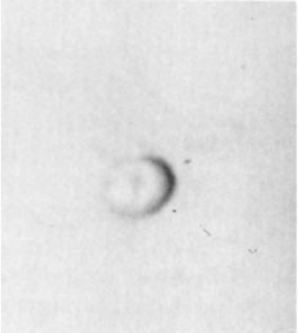


Figure 7–12. Molluscum contagiosum.

is usually skin-colored; however, transparent lesions are described and commonly referred to as "water warts." The feature that is most characteristic of molluscum contagiosum is central umbilication. This usually indicates the presence of a mature molluscum. Occasionally, lesions are surrounded by inflammatory reactions[261] which may suggest furunculosis, eczema, or other diagnoses. Most lesions are asymptomatic, although the aforementioned inflamed ones might be somewhat painful.

Treatment. Left alone, molluscum contagiosum resolves within an 18-month period. As in the case with other warts, the problem is that new lesions may erupt during this period of time and it may be several years before the patient is rid of these irritating and cosmetically unattractive lesions. Since the treatment is simple, it is often preferable to curette these lesions when they are diagnosed. This is done by a small incision made at the umbilicated portion of the lesion (usually painless) and extrusion or curettage of the curd-like material present in the center of these lesions. This material contains virus and should be handled with care. Viral inclusion bodies can be seen if the material is spread on a glass slide and examined microscopically. This treatment is usually curative. When multiple lesions are present, it might be preferable to apply collodion or some other topical irritant to stimulate inflammation, a process that hastens disappearance of the lesions, as noted with condyloma as well.

Prevention. These pox viruses spread by direct contact. The lesions should be considered infectious, as should the curd-like material contained within them. Although spread is slow and inefficient, direct contact through playing or sexual intercourse are usually responsible. In view of these facts, prevention of these lesions depends on recognition and appropriate procedures to avoid direct contact.

Roseola Infantum

Roseola infantum, also known as exanthem subitum, is a febrile illness associated with rash and is frequently seen in the fall and winter months. Infants over 3 months of age and under 4 years are most commonly affected. The condition may represent the expression of several viral agents, such as parainfluenza, enterovirus, and adenovirus. It is also probable, however, that in many cases, as yet unidentified agents may be responsible. A recent report from Japan suggests that rotaviruses may sometimes be associated with this syndrome.[272]

Clinical Manifestations. After an incubation period estimated to be between 5 and 15 days, this mild contagious condition manifests predominantly as fever. For 3–5 days, parents and physicians worry about these infants, since they have no localizing signs, but run relatively high temperatures (37.7°–40°C). A variety of nonspecific signs and symptoms may be noted, including anorexia, irritability, and, occasionally, vomiting and diarrhea. Coryza and upper respiratory signs, with mild inflammation of the throat, tonsils, and anterior cervical lymph nodes have also been reported. Some periorbital edema may be seen as well. The major point is that these patients do not have an identifiable focus of infection and often appear quite content and happy when antipyretics are administered and they become at ease with the examiner.

The diagnosis usually becomes obvious when the rash appears after the third to fifth day of fever. Within a few hours, nonpruritic macular or maculopapular lesions appear on the trunk, arms, and neck, and the patient's temperature falls quite suddenly. The rash may also involve the face, and rarely lasts longer than 3 days. The white blood cell count is usually in the range of 5–10,000 cells/mm^3 with a relative lymphocytosis, but this is not specific.

Prognosis. The importance of this disease lies mostly in the confusion that may arise in differential diagnosis with otitis media or other infectious conditions with similar presenting signs and symptoms. One can imagine that on the second or third day of high fever the patient could easily have erythematous tympanic membranes, suggesting a diagnosis of early otitis media. The administration of an antibiotic at this point would predictably result in a rash syndrome with defervescence 1 or 2 days later. It is easy to understand how these circumstances can be misinterpreted as a positive response to the antibiotic therapy, but an allergic reaction of the host. This type of diagnostic pitfall is frequent with roseola.

One serious complication of roseola is febrile convulsion precipitated by the temperature rise, usually observed in the early part of the illness. Although a few cells have been seen in the cerebrospinal fluid of such patients (5–10 mononuclear cells), most have normal cerebrospinal fluid and no evidence of neurologic involvement.

The disease is not highly contagious, except in family units where siblings of the appropriate age are exposed. It is presumed to be infectious, and the challenge lies in defining an etiology if, in fact, only one cause is responsible.

Erythema Infectiosum

This condition, also known as "fifth disease," is of uncertain etiology. Several enteroviruses, respiratory viruses, and rubella viruses have been isolated from these patients; however, no single agent has been implicated as causative in the majority of cases.[20] Analysis of two recent outbreaks in England revealed a high prevalence of serologic reaction to human parvovirus.[7]

Clinical Manifestations. The disease is mild and self-limited. It occurs in outbreaks predominantly in the winter and spring months and affects mostly school-age children.[40] However, individuals in all age groups may manifest some of the signs. After an incubation period estimated to be between 4 and 14 days, the child develops a "slapped cheek" appearance due to skin erythema over both cheeks.[116] Low-grade fever is present in only 15% of children and in 50% of adults. At 1–14 days later, the rash usually spreads to the trunk and buttocks, and later becomes lace-like, or reticular, in appearance. This rash may come and go for several weeks. Complications or specific extracutaneous signs are extremely rare with this rash syndrome, although as many as 50% of adults complain of arthralgia and may have joint swelling. Encephalopathy has been described in a 9-month-old.[132] Outbreaks indicate that this condition is probably contagious in nature; however, specific isolation procedures are seldom required.

Mucocutaneous Lymph Node Syndrome (Kawasaki Disease)

Epidemiology. Since its description in 1967 by Kawasaki, over 30,000 cases of mucocutaneous lymph node syndrome (MLNS) or Kawasaki disease have been reported worldwide.[212] The condition is most prevalent in the winter and spring months in North America. In two recent outbreaks in North America it was more common in middle and upper socioeconomic classes.[33]

Pathogenesis/Etiology. Theories of pathogenesis have been generated from epidemiologic, genetic, and pathologic considerations. The sudden onset of a febrile illness, outbreaks, history of associated respiratory infection, and leukocytosis and an elevated erythrocyte sedimentation rate suggest that MLNS has an infectious basis. A respiratory virus or virus-like organism may act as a triggering event, and serologic evidence of MLNS[281] with Rocky Mountain spotted fever has also been reported.[136] This might occur by a direct toxic effect of the microorganism in genetically predisposed hosts, or by the infectious agent modifying the host response to other antigens (infectious micro-organisms, toxins, drugs, environmental antigens, etc.) or stimulates a host-autoimmune response. Rug shampoo, house dust, mites, and other causes have been postulated.[85] Evidently, genetic features also are important, since Japanese patients seem more prone to this illness, and at least two haplotypes have been described—HLA-Bw22 is most prevalent in Japanese patients[166] and HLA-Bw51 in children in New England.[176]

Clinical Manifestations. Although most patients have at least five of the cardinal features outlined in Table 7–12, clinical features of the disease

TABLE 7–12. Kawasaki Syndrome (Mucocutaneous Lymph Node Syndrome): Diagnostic Clinical Features

History/Physical Examination
Fever ≥ 5 days
Conjunctivitis
Labio-oro-pharyngitis
Edema/erythema of peripheral extremities (followed by desquamation)
Rash: maculo-papular erythematous
Lymphadenopathy

are diverse. These are often ill-appearing children, usually 5 years of age or younger. In the early stages many features suggest meningococcal disease, Rocky Mountain spotted fever,[31] or severe drug hypersensitivity reactions.[332] In older patients, acute enteroviral infections, streptococcal and staphylococcal infections, and toxic shock syndrome may have somewhat similar presentations (Table 7–13). In fact, hemolytic uremic syndrome[100] and shock requiring dopamine therapy have been described.[208] Fever is usually prolonged for a week to 10 days, and in some patients may last 2–3 weeks. Bulbar conjunctivitis, periorbital edema, and other ocular manifestations may be present,[231] including retinitis[317] and uveitis.[184] Mucosal involvement consists of reddening, swelling, and fissures, particularly of the lips; vesiculation and deep ulcerations are unusual and they serve to differentiate this condition from Stevens-Johnson syndrome, primary herpes stomatitis, and other causes of mouth ulcers. Retropharyngeal mass has been reported in a child with this syndrome, probably due to lymph node enlargement.[39]

The rash described in this syndrome is extremely variable, ranging from faint macules to a diffuse scarlatiniform appearance. Often the palms and the soles are also reddened, although it is rare to note distinct macules, papules, or petechiae in these locations. These features, if present, should more likely suggest Rocky Mountain spotted fever, drug hypersensitivity, secondary syphilis, atypical measles, or enterovirus (particularly coxsackie) infection. Lymphadenopathy is prominent and usually cervical in distribution, although not as marked as in severe streptococcal pharyngitis or infectious mononucleosis. Diffuse swelling of the fingers and toes is particularly characteristic (Fig. 7–13), as is the periungual desquamation (Fig. 7–14). The skin comes off in large pieces, usually during convalescence in the second to third week of illness, and is not painful for the patient. This is somewhat different than the brawny more superficial desquamation seen after streptococcal or staphylococcal infections.

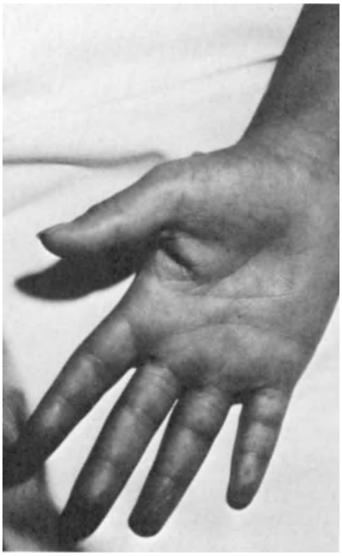
Cardiac manifestations may occur in up to 60% of children in some outbreaks.[208]

TABLE 7–13. Mucocutaneous Lymph Node Syndrome: Differential Diagnosis

- Scarlet fever
  - Streptococcal
  - Staphylococcal
- Toxic shock syndrome
- Meningococcemia
- Rocky Mountain spotted fever
- Leptospirosis
- Measles
- Infectious mononucleosis
- Enteroviral infection
- Erythema multiforme
- Drug hypersensitivity
- Infantile polyarteritis nodosa
- Systemic lupus erythematosus
- Rat-bite fever
- Tick typhus
- Toxoplasmosis
- Cytomegalovirus infection
- Reiter syndrome
- Juvenile rheumatoid arthritis
- Behçet disease
- Acrodynia

Pathology. The pathology noted in this condition is mostly that of vasculitis.[114] Small vessels are initially affected, with a mononuclear cell infiltrate around arterioles, capillaries, and venules. In the second and third weeks of illness, medium-size arteries are involved and aneurysmal dilatations may occur. These are most clinically significant when seen in coronary arteries and may be the cause of death in as many as 3% of these patients. The presence of coronary artery aneurysms is most readily defined by means of two-dimensional echocardiography and can be noted in up to 30% of cases.[228] Electrocardiographic findings may include prolongation of the PR and QT intervals and flattening of the T-waves, and other evidence of pericarditis and myocarditis may also be present. The diffuse vasculitis that occurs in this condition may explain the diverse multisystem involvement noted. Thus, hepatitis with jaundice, aseptic meningitis, and gastrointestinal signs have been reported.[212] Arthralgia may be noted in older patients, although arthritis is unusual. Severe abdominal pain in these patients may herald the presence of hydrops of the gallbladder, best diagnosed by sonography.[292] This complication has been noted with unusual frequency in MLNS.

Diagnosis. Diagnosis is based on exclusion. In the early stages, both clinical and laboratory studies are often needed to exclude the presence



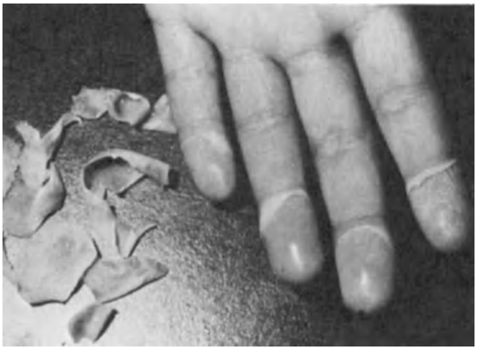


Figure 7–14. Characteristic desquamation often noted in the convalescent stage of mucocutaneous lymph node syndrome.

◁

Figure 7–13. Swelling of fingers in patient with mucocutaneous lymph node syndrome.

of meningococcemia, streptococcal and staphylococcal disease, leptospirosis, enteroviral infection, and infectious mononucleosis. Historical features may suggest drug hypersensitivity. Thus blood cultures, white blood cell count, erythrocyte sedimentation rate, and lumbar puncture may be indicated in some patients. Historical features are essential in suspecting measles, atypical measles, drug hypersensitivities, Rocky Mountain spotted fever, and rat-bite fever. At certain stages it may be necessary to consider autoimmune diseases more seriously, although most patients fall more clearly into the MLNS classification as the clinical course evolves.

Laboratory features of MLNS include nonspecific signs of inflammation, such as leukocytosis and elevated erythrocyte sedimentation rate and C-reactive protein. These are not consistent findings, except for the Wintrobe sedimentation rate, which is often in the range of 50–70 mm/h. Thrombocytosis is present in many of these patients and is helpful in differentiating the condition from Rocky Mountain spotted fever, although this feature may not be present until the end of the first week of illness.

Treatment. Despite extensive investigations and experience with the condition since 1967, no consistent etiology or triggering event has been delineated. Thus, discussions of therapy remain rather empirical. What is clear is that adrenal corticosteroids should not be used because they tend to increase cardiac involvement and the severity of thrombocytosis.[167] Aspirin therapy is more controversial. One Japanese controlled study suggests that this form of therapy does not alter the course of clinical illness, although others, with considerable experience with this condition, claim amelioration of the acute febrile component.[151] If aspirin is to be used, its contraindications should be kept in mind, and it should be used in sufficient dosage (up to 100 mg/kg/day) to maintain a serum concentration of 20–30 mg/dl. Some of these patients seem to absorb aspirin less well than others, so that monitoring of serum salicylate concentrations is necessary and high dosage may be required in the initial stages. When used, it is suggested that aspirin be continued until the erythrocyte sedimentation rate returns to normal. This may take up to 6 weeks. The acute stage of illness is usually over by the end of the second week, although complete convalescence may not occur until 6 weeks. A reasonable plan is to continue aspirin therapy until the platelet count and sedimentation rate return to normal, and to repeat the echocardiogram at 6 and 12 months after onset, if it was initially abnormal.[53]

Prognosis. The prognosis is excellent in most patients; however, coronary artery aneurysms may lead to thrombotic myocardial infarction as mentioned above. Although the majority of aneurysmal ruptures and thrombosis occur within the first 3 months after the onset of this illness, rupture of coronary and hepatic arteries has been reported 3 years after the initial illness.[194] The relationship of this disease to coronary artery disease later in life and to other vasculitides remains speculative.[276] Certainly the definition of arteritis in these patients requires careful followup and further investigation.

Bacterial Skin Infections

Furunculosis/Abscess

Staphylococcal infections may take many forms. The commonest expression of staphylococcal infection is probably the "pimple," which can occur anywhere in the body and is usually referred to as folliculitis or furunculosis. Other terms also used include abscess or carbuncle, when the lesion is larger, and pyoderma. In any event, staphylococcal pyodermas are extremely variable in location, size, frequency, and pathogenesis. Acute disease is commonly seen with poor hygiene and in areas of frequent trauma, where Staphylococcus may contaminate minor wounds, or both. Some patients have recurrent disease, which is extremely variable in frequency and severity. In these cases, the staphylococcal lesions are often most concentrated in hairy areas. Perhaps this is related to the frequency of hair follicles in such sites.

Cutaneous abscesses are not always staphylococcal, as noted in decubitus ulcers, acne vulgaris, and wound infections; papulopustular Pseudomonas folliculitis acquired in contaminated spas is an excellent example.[130] Anaerobic bacteria and mixed infections may be present in paronychial, scaly, and perineal lesions.[43] A variety of infections, including cutaneous myiasis, a larval infestation, may mimic furunculosis.[128]

Pathogenesis. The most important host defenses involved in the pathogenesis of staphylococcal infections are the polymorphonuclear leukocyte and serum opsonins. The latter may consist of specific antibody or nonspecific serum proteins, and complement may play a role in the enhancement of phagocytosis when these antibodies react with their target antigens. Knowledge of these host factors is important in investigating possible underlying conditions associated with frequent and severe recurrences of staphylococcal furunculosis. Thus, congenital and acquired immunocompromised states, and phagocyte disorders (e.g., chronic granulomatous disease, Chediak-Higashi syndrome, Job syndrome, and neutropenias) should be considered and appropriate historical and, laboratory features examined. Abnormal locations (e.g., perirectal) and anaerobic and enteric flora often characterize the abscesses acquired by such patients.[82] Patients with underlying skin diseases, such as ichthyosis, seborrheic dermatitis, and eczema, are prone to staphylococcal skin colonization and pyodermas as well. In some children recurrent infections are associated with an increase in serum IgE levels, eosinophilia, eczema, and chemotactic deficiency.[279] Other associated features include a familial history of recurrent staphylococcal infection, an increased serum concentration of IgA, and red hair.[280] This is in contrast to the majority of patients with staphylococcal infections who have increased or normal chemotactic responses.[51] Adults with diabetes mellitus are also prone to staphylococcal infections. This is not usually a problem with children, possibly because these infections are related to the microangiopathy associated with adult onset diabetes.

Clinical Manifestations/Diagnosis. Clinical manifestations and diagnosis of staphylococcal pyoderma usually present little problem. The classic evolution of these lesions is from painful macules and papules to pustules and, if coalescent, abscesses. The pus in these lesions usually contains many neutrophils and gram-positive cocci. Gram stain and culture may occasionally reveal unexpected pathogens, requiring different approaches to management and therapy. These tests are mandatory in patients with abnormal defense mechanisms, in whom a wide variety of pathogens may be causative, and in patients with recurrent disease, infections with atypical locations, and spread despite appropriate therapy. Ecthyma gangrenosum, usually seen in neutropenic patients, is characterized by painful papules which then rapidly progress to hemorrhagic vesicles and necrotic ulcers. *Pseudomonas aeruginosa* is the commonest cause;[175] however, other bacteria, including *Aeromonas hydrophila,*[111] may be responsible.

Therapy. The vast majority of cases of staphylococcal furunculosis can be managed by simple topical and systemic therapies. Topically, warm soaks and washing with hexachlorophene-containing soaps are useful. The use of these soaps should be restricted to acute episodes and limited to affected areas, since hypersensitization and systemic absorption with attendant toxicity may result. This is particularly true for newborns (Chapter 3).

Recurrent Furunculosis. When lesions are recurrent, large, or widespread, systemic administration of dicloxacillin 75 mg/kg/day for 5–7 days will result in rapid resolution. The earlier such treatment is begun, the better the result. In fact, in patients with recurrent furunculosis, this is the treatment of choice and should be started at the earliest sign (macules and papules) of a recurrence. In this way, lesions can often be aborted before they reach the pustular stage. Patients who are allergic to penicillin can be given cephalexin in the same dosage. Some patients have large, painful lesions which will also require incision and drainage. Appropriate hygienic practices, including frequent changes of clothing and linens that come into direct contact with the lesions, as well as adequate laundering, are also important. Daily bathing is also helpful.

What about patients with severe and frequent recurrences? The condition is rarely associated with systemic invasion, but can be extremely distressing because these lesions are painful, and sometimes may be in dangerous sites (e.g., eye, over a joint, periurethral). In these patients, careful consideration of predisposing illnesses should be given (see Pathogenesis above). Attention to hygiene, nail-cutting, and occupational exposure is important. These patients should be warned against food handling and caring for ill patients, especially during periods when active skin lesions are present. An appropriate initial laboratory screen for such patients includes hemoglobin and peripheral white blood cell count, including morphology of the white blood cells, a platelet count, quantitative serum immunoglobulins, complement assay, fasting or 2-h postprandial blood glucose, urinalysis, and a careful family history and clinical examination. It may be worthwhile to obtain a nitroblue tetrazolium test or otherwise assess the capacity of phagocytes to kill bacteria. Involvement of lymph nodes, viscera, and other extracutaneous sites is a clue to immune deficiency in such patients which may involve granulocytes[11] or immunoglobulins.[314]

It should be remembered that in many of these patients this condition is self-limited over a period of months to years. Children who acquire this condition before puberty rarely suffer with it after they reach their teenage years. The course and duration are difficult to predict, hence, many claims about successful therapeutic modalities fill the lay and scientific literature. Techniques such as bacterial interference have been used to arrest epidemics of staphylococcal furunculosis in closed populations and have also been applied to individuals and families with recurrent disease.[298] Occasionally, this can backfire and the implanted "nonpathogenic" *Staphylococcus epidermidis* may invade and cause serious infection.[146] This approach, elimination of nasal and other body carriage sites, and the use of autogenous vaccines should be considered experimental and should be restricted to centers where phage-typing and tests of phagocytic and opsonic functions can be carried out. The vast majority of these patients have an excellent prognosis, no underlying disease, and respond well to hygienic measures and specific antistaphylococcal therapy.

Cellulitis

Cellulitis is defined as inflammation of the skin and subcutaneous tissues. The entity may clearly be related to trauma, as seen after a variety of superficial skin lesions or may arise de novo, presumably after hematogenous spread. Examples of the former include staphylococcal and streptococcal cellulitis around penetrating and scratch wounds, and of the latter, extremity or periorbital cellulitis without history or evidence of trauma. Periorbital cellulitis is discussed in Chapter 4 and cellulitis in newborns in Chapter 3.

Etiology. The principal causes of cellulitis are listed in Table 7–14. Inflammation due to either infectious or noninfectious causes such as eosinophilic cellulitis may be seen.[277] Most cases in normal hosts at all ages

TABLE 7–14. Causes of Cellulitis

- Infectious
  - *Staphylococcus aureus*
  - *Streptococcus pyogenes*
  - *Haemophilus influenzae*
  - Other bacteria
    - *Streptococcus pneumoniae*
    - *Pseudomonas aeruginosa*
    - *Clostridia sp.*
- Noninfectious
  - Frostbite
  - Burns
  - Trauma
  - Home remedies (e.g., cupping)
  - Foreign bodies
  - Vascular malformations
  - Lymphedema

are due to *Staphylococcus aureus* or *Streptococcus pyogenes*. Patients between the ages of 6 months and 2 years are more likely to have cellulitis due to *Haemophilus influenzae* regardless of the location. One exception is cellulitis in the perianal area, where gram-negative bacteria and group A Streptococcus may be causative.[139] Host factors may also be important, as illustrated by the relative frequency of gram-negative bacterial causes (e.g., *Pseudomonas aeruginosa*[259] and *Serratia marcescens*[38]) of cellulitis in leukemic and other immunosuppressed patients. A rare cause is erysipelothrix in patients handling crabs or fish nets.

Patients exposed to cold weather may develop frostbite of the cheeks. This has also been described after children have kept popsicles on the inside of the cheek for a long period of time ("popsicle panniculitis").[90] Sometimes, cultural customs include home remedies for treating fever, including "cupping" or the Vietnamese custom of scratching the back.[75] These may, at times, produce skin lesions that are confused with infectious cellulitis. When cellulitis is recurrent, and the cause cannot be found, factitious events such as self-inoculation should be suspected.[301]

Clinical Manifestations. Cellulitis is usually manifest as a swollen, red, tender area of the skin (Fig. 7–15). The subcutaneous tissues may also be involved, but because of fluctuation there is a tendency to classify the lesion as an abscess and to suggest that *S. aureus* may be causative. Since

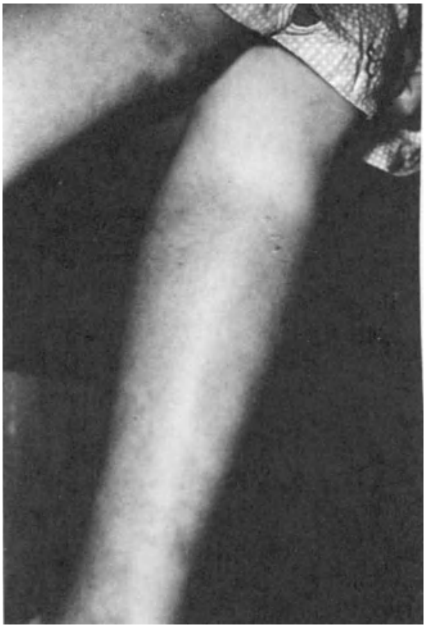


Figure 7–15. Streptococcal cellulitis. For color reproduction of this figure see frontmatter.

drainage is indicated earlier in the latter situation, this differentiation may be important. Patients with cellulitis often have low-grade fever and anorexia, irritability, and malaise. In infants with this condition, it may be difficult to differentiate isolated cellulitis alone from systemic infection due to hematogenous spread. Hence, it is often necessary to perform a lumbar puncture to rule out the presence of meningitis.[121] Even if meningitis is not present at the outset, it should be considered in patients with atypical courses after suspected hematogenous cellulitis.

Cellulitis may occur in any part of the body, although lesions of the face and extremities predominate. Buccal cellulitis is usually unilateral, but bilateral involvement has been reported.[182] Although violaceous discoloration has been mentioned frequently as suggestive of *Haemophilus influenzae* infection, this may also be seen with other causes, including *S. pneumoniae.*[308] We have seen a leukemia patient with marked cellulitis of the extremities with unusually painful lesions due to *P. aeruginosa.*[259]

Specific clues to etiology are sometimes present. This includes erysipelas, in which the margins of the cellulitis are raised and clearly demarcated. This indicates group A *Streptococcus pyogenes* as the probable cause; however, Haemophilus can also produce this effect.[294] Facial erysipelas may be seen in immune-deficient hosts,[63] and may be due to Streptococcus or Erysipelothrix,[180] commonly called erysipeloid. Similarly, gas bubbles in the skin indicate the presence of clostridia or mixed anaerobic and aerobic gas-forming bacteria. A careful search for subcutaneous necrosis and foreign bodies, as well as aggressive therapy, are indicated. Facial cellulitis associated with dental abscess or skin breaks are generally due to *Staphylococcus aureus* or *Streptococcus pyogenes,* whereas young children without a port of entry and buccal cellulitis usually have bacteremia due to *Haemophilus influenzae.*[50]

Diagnosis. Although the vast majority of cases of cellulitis in infancy and childhood are due to *S. aureus, Streptococcus pyogenes,* and *H. influenzae,* the bacterial causes of these infections can be diverse, and simplification of therapy may be facilitated by accurate etiologic diagnosis. Hence, both needle aspiration of the advancing margin of the cellulitis and blood cultures are recommended.[106] In such cases, a 21–23-gauge needle can be introduced into the advancing margin of the skin and subcutaneous tissues of the cellulitis without any local anesthetic. If any fluid is obtained from the subcutaneous tissue at this site, it should be gram-stained and cultured. If fluid is not obtained, then approximately 0.1 ml of normal nonbacteriostatic saline should be injected into the area and reaspirated (the syringe should be prepared with this material before the aspiration). Gram stain of this material may suggest the etiology, and culture will confirm it, and provide specific guidelines for antibiotic therapy.[275] Blood cultures are most useful if performed after this procedure, since liberation of bacteria into the blood stream may occur with needling. A search for

Haemophilus and pneumococcal antigen in the urine and serum of such patients is also useful.[123]

Therapy. Initial therapy of cellulitis in infants and children has been simplified by the development of broad-spectrum cephalosporins. Drugs such as cefotaxime, cefoperazone, and ceftriaxone can be used because they will adequately inhibit the growth of the common causative agents, regardless of the production of antibiotic-inactivating enzymes.

In children over the age of 6 years, who are not very toxic, penicillin therapy can be instituted, since group A *Streptococcus pyogenes* is the most likely pathogen. Progression of illness and fever should suggest the possibility of infection with *Staphylococcus aureus* or another pathogen and indicate the need for further diagnostic studies and alternate antibiotics. Once the etiology is more specifically known, the antibiotic program can be simplified, the cost reduced, and the route improved. For example, oral penicillin would be appropriate for nonpenicillinase-producing *S. aureus* and amoxicillin for β-lactamase-negative *H. influenzae.* The vast majority of patients become afebrile within 24–48 h of institution of antibiotic therapy. If they are not, one should search for extracutaneous complications and other infectious foci. The total duration of therapy in these patients is usually around 7 days. The patient should be afebrile and clinically improved for at least 48 h before discontinuation of antibiotics. Underlying causes for cellulitis should also be considered, such as host factors, trauma, and exposure to group A Streptococcus in contacts. Extensive and recurrent cases of cellulitis need to be investigated for nutritional deficiencies, underlying or predisposing illnesses, and child abuse.

Impetigo

Epidemiology/Pathogenesis. Superficial skin infections are frequently seen in patients with skin trauma, poor hygiene, and malnutrition. In some populations, such as certain American Indians and Eskimos, and in Trinidad, this condition is endemic. Outbreaks may involve nephritogenic strains of group A *Streptococcus pyogenes,* leading to poststreptococcal glomerulonephritis in considerable numbers of children. In endemic populations, the infecting strain of group A Streptococcus first colonizes the normal skin;[76] this occurs approximately 2 weeks before impetigo is noted. Subsequent spread to nose and throat sites is common after both normal skin colonization and the appearance of impetigo. Although group A *Streptococcus pyogenes* causes the majority of typical crusting impetigo (also called streptococcal pyoderma), *Staphylococcus aureus* is often present as well; in this case, the latter is thought to be a secondary invader. Most important, treatment directed at Streptococcus will bring about clinical cure. *S. aureus,* the other major cause of pyoderma, usually causes localized abscesses or, in the case of impetigo, bullous lesions.

Clinical Manifestations. Impetigo can be roughly divided into two major types. In the first, most common type, weeping crusted lesions are seen, most frequently over the extensor surfaces of the extremities (Fig. 7–16). Yellowish discharge is often present, and pruritus, tenderness, mild fever, and localized lymphadenopathy may be noted. These lesions are classically due to group A *Streptococcus pyogenes.*

The second type is called bullous impetigo. This is an important clinical differentiation, since these blister-like lesions should be presumed due to *S. aureus* and therapy needs to be directed against that organism. The bullous nature of the lesion is thought to be due to the local production of exfoliatoxin. This is probably the mildest form of toxic epidermal necrolysis or staphylococcal scalded skin syndrome. Whether or not these lesions remain localized may be related to the inoculum, the amount of exfoliatoxin produced, or other characteristics of the host-parasite relationship. Both types of impetigo are seen most commonly in toddler and school-age children, although bullous impetigo has been reported throughout childhood, adolescence, and adulthood.[88]

In rare cases, group A *Streptococcus pyogenes* can cause a superficial blistering lesion over the anterior fat pads of the distal phalanx of fingers or thumbs, called streptococcal dactylitis. Incision and drainage of a thin white pus may hasten recovery, along with systemic antibiotic therapy.[135]

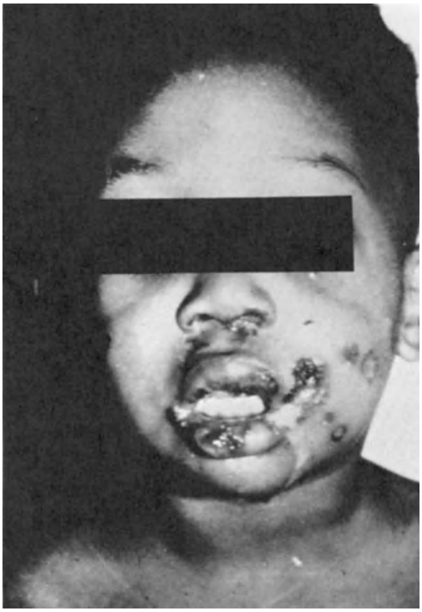


Figure 7–16. Impetigo.

Diagnosis. In most cases the diagnosis of impetigo can be made by examination of the lesions. It is important to remember that other household and day-care center contacts may also have similar lesions. It is also useful to keep in mind that some of these children come from families where hygiene and nutrition may be substandard; thus it is worthwhile to examine for associated conditions, including scabies, parasitic infestations, iron deficiency anemia, and psychosocial dysfunction. When the appearance of the lesions is obscure, or if there is resistance to therapy (compliance is often a problem in the latter circumstance), culture of the lesions may be useful. In such circumstances, scraping of the base of the lesions is usually necessary when looking for Streptococcus. Aspiration of bullous fluid will usually yield *S. aureus.* Occasionally, other pathogens may be detected. In single lesions, with foreign bodies, and in chronic lesions, other etiologies such as tuberculosis, cutaneous histoplasmosis, atypical mycobacterial infections, nocardiosis, cutaneous diphtheria, and scabies may be responsible.

Serologic response to streptococcal impetigo are best measured by anti-DNase B or hyaluronidase antibodies, since an anti-streptolysin O antibody response is seen much less consistently with skin infection than after pharyngeal streptococcal infection.

Therapy. Phenoxymethyl penicillin 50,000 units/kg/day divided three times daily for 7–10 days is effective in > 90% of cases. Erythromycin 50 mg/kg/day divided twice or thrice daily is also highly effective and may be preferred in situations where a bullous component is present or there is confusion about the classification of the lesion into streptococcal or staphylococcal types.[72] It should be remembered, however, that in the U.S. approximately 5% of group A streptococci are resistant to erythromycin;[150] this figure may be higher in other areas, such as Japan. A similar percentage of staphylococci may also be resistant to erythromycin, hence therapy with dicloxacillin 50 mg/kg/day, divided q.i.d. (cephalexin in patients allergic to penicillin) is preferable in treating bullous impetigo. Incision and drainage are rarely needed, except with large painful abscesses or streptococcal dactylitis (see above). Daily baths, improved hygiene, trimming of nails, and nutritional advice are also useful; however, it is unnecessary to prescribe topical antibiotics or hexachlorophene and the patient need not add the additional discomfort of scrubbing these tender lesions.[268] Treatment of contacts is also important and, of course, improvement in hygienic standards may yield the most rewarding long-term results.

Prognosis/Complications. In general, children with impetigo respond to appropriate antibiotic and hygienic therapy within 3–4 days, and lesions are completely healed by 10 days. Some patients may have localized abscesses that take longer to resolve, particularly when these are multiple, and the patient is otherwise debilitated. Localized lymphadenopathy may occasionally progress to suppuration, as may some of the skin lesions. Bacteremia and extracutaneous infectious foci are rare with streptococcal impetigo, but may be more commonly seen when staphylococcal abscesses complicate the case, or when these lesions occur in immunocompromised patients.

One of the gravest complications of streptococcal impetigo is glomerulonephritis, which occurs an average of 3 weeks after the skin lesions.[162] Although it is speculated that early treatment of streptococcal skin infections might prevent this complication, there is little clinical evidence to support this. Fortunately, the prognosis is excellent in the vast majority of cases with poststreptococcal glomerulonephritis; however, some patients may have severe hypertension and azotemia in the acute stage.

Bullous impetigo may spread over large portions of the body and some patients may actually develop the full-blown staphylococcal scalded skin syndrome. Others, if untreated, may also develop toxic shock syndrome, particularly in older patients. For such a complication to occur, it is theorized that the infecting Staphylococcus should produce both exfoliatoxin and other toxins reported to play a role in the pathogenesis of toxic shock syndrome. Early antibiotic treatment of bullous impetigo should avoid these complications.

Staphylococcal bacteremia and extracutaneous foci of infection are always a threat to patients with pyoderma. When these complications occur with apparently minor skin lesions, it is worthwhile to consider specific or general immune deficiencies in such hosts.

Rarely, bullous lesions can become superinfected, as we recently noted in an infant with extensive cutaneous herpes simplex infection.[134] Clues to this diagnosis were herpes labialis in the mother, and failure to improve after dicloxacillin therapy.

Staphylococcal Scalded Skin Syndrome

The extension of bullous impetigo to a generalized exfoliative skin condition is important in the pathogenesis of the staphylococcal scalded skin syndome in some patients. In newborns this has been called "Ritter disease," and in adults, "Lyell disease." Use of these eponyms has created some confusion. In newborns, as in bullous impetigo, polymorphonuclear leukocytes and bacteria are often present in the skin lesions; however, unlike bullous impetigo, it frequently has a bacteremic component. Staphylococcal scalded skin syndrome rarely has either feature, since the skin lesions usually contain serous fluid and are rarely associated with bacteremia. Similarly, the term "Lyell disease" has been applied to illness due to either *Staphylococcus aureus* or hypersensitivity reactions to a variety of antigens. These acute exfoliative conditions can be roughly divided into those that are mainly due to *S. aureus* (Ritter disease of the newborn, bullous impetigo, staphylococcal scalded skin syndrome, toxic shock syndrome), and those that are due mainly to hypersensitivity reactions (toxic epidermal necrolysis, Lyell disease, erythema multiforme, Stevens-Johnson syndrome). Some of the characteristics that can be used to differentiate these conditions are listed in Table 7–15.

Pathogenesis/Epidemiology. Staphylococcal scalded skin syndromes generally affect young children under the age of 5, although individuals in all age groups can be involved. Sometimes, immune deficiencies, such as decreased chemotaxis and T cell hyporesponsiveness, characterize the condition when it occurs in adults.[243] It is now recognized that some conditions, such as bullous varicella, actually represent staphylococcal superinfection of chickenpox lesions. The infecting staphylococci produce a toxin that is systemically absorbed, and capable of inducing bullae locally and at a distance from the original colonization sites.[211] When a small amount of toxin is produced, or the host is able to confine the effects of the toxin locally, or both, the lesions may manifest only as bullous impetigo. When the host is unable to confine either the bacteria or the toxin, such as seen in newborns, generalized exfoliation and septicemia may occur. In most normal infants and children, the toxin is absorbed systemically from staphylococcal colonization sites in the upper respiratory tract, or occasionally from other mucosal sites or minor lesions, and there is generalized erythroderma and exfoliation. Although sporadic cases are most frequent, nosocomial spread in a nursery has been reported.[107] An exfoliative dermatitis has also been described due to an epidermal toxin produced by Staphylococcus, which causes subepidermal

TABLE 7–15. Features of Staphylococcal Scalded Skin Syndrome (SSSS) Compared to Severe Erythema Multiforme (EM)

Features	*SSSS*	*EM*
Cause	*Staphylococcus aureus*	Hypersenstivity reaction to drugs/other antigens
Age	< 5 years	All ages (most > 5 years)
Mucous membranes	Spared	Diffuse ulcerations
Skin	Tender No bleeding	Nontender Cutaneous bleeding
Mortality	< 5%	25–50%
Duration	7–10 days	2–6 Weeks
Scarring	No	Yes
Histopathology (cleavage plane)	Intraepidermal	Epidermal-dermal
Treatment	Penicillinase-resistant penicillin	Supportive

cleavage. The clinical picture has features that overlap both the scalded skin and toxic shock syndromes.[56]

Etiology. The major causative organism is *S. aureus*. Although it was originally thought that phage group II was exclusively responsible for this condition, toxin production has subsequently been demonstrated in several phage groups. Considering that production of this enzyme can be plasmid-mediated, this is not surprising.

Clinical Manifestations. Some patients have a prodrome, consisting of malaise, anorexia, and mild fever. In others the onset of disease is more abrupt. There is a generalized erythematous rash which progresses to flaccid bullae (Fig. 7–17). The skin is extremely tender and the patient often toxic with high fever. There is a positive Nikolsky sign. This means that the skin in normal-appearing areas (these areas may be red but do not have bullae) will desquamate when rubbed. Other clinical features are outlined in Table 7–15.

The differential diagnosis of staphylococcal scalded skin syndrome in its early stages includes sunburn, secondarily infected eczema, and scarlet fever. In later stages, confusion with hypersensitivity-mediated exfoliative skin disorders is common. In its full-blown stage, severe erythema-multiforme is the major differential diagnosis. In teenagers and young adults, toxic shock syndrome may be confused with this condition, although many of the features of toxic shock syndrome are lacking in staphylococcal scalded skin syndrome. These are mainly hypotension, disseminated intravascular coagulation, gastrointestinal symptoms, and disorientation. The rash in toxic shock syndrome is finely desquamative and usually appears in early convalescence, whereas the rash in staphylococcal scalded skin syndrome is bullous and present in the acute stage of illness.

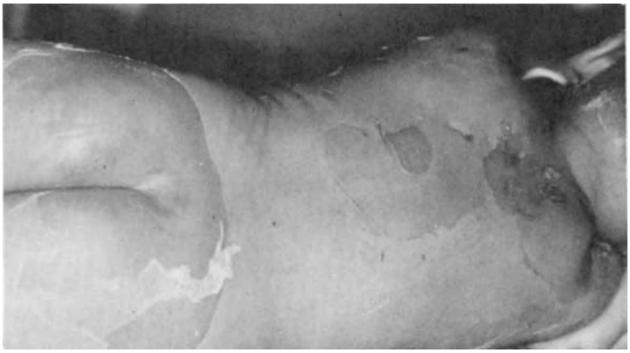


Figure 7–17. Staphylococcal scalded skin syndrome.

Diagnosis. The diagnosis of this condition is suggested by its clinical appearance, since bullous eruptions associated with fever are due mainly to hypersensitivity or staphylococcal infections. Objective differentiation of these two conditions can be made by skin biopsy, since the cleavage plane is in the epidermal layer in Staphylococcus-induced exfoliation, but in the deeper layers when hypersensitivity is responsible.[200] *S. aureus* can be cultured from the skin lesions in newborns and in patients wtih bullous impetigo, but usually only from the nose, nasopharynx, or other mucous membrane sites in the older patient with staphylococcal scalded skin syndrome. When there is associated conjunctivitis, rhinitis, or other mucosal or skin lesions, these usually will also yield the organism. Although the same phage type of Staphylococcus may be present in the upper respiratory tract of household contacts, they rarely manifest disease.

Progress is being made toward the development of commercially practical assays for staphylococcal exfoliatoxin.[331] Assay for this antigen or its antibody, however, is rarely necessary for clinical diagnosis.

Therapy. Penicillinase-resistant penicillins are the drugs of choice for the treatment of this condition. In patients who are able to take drugs orally, dicloxacillin 75 mg/kg/day divided q 6 h is effective. In patients allergic to penicillins, cephalexin can be used. Parenteral alternates include nafcillin, oxacillin, and cephalothin. Pooled human immunoglobulin does not contain enough antibody against the toxin and would not be expected to be useful therapeutically.[165] Similarly, corticosteroids have been found to have a detrimental effect on the outcome of Staphylococcus-induced exfoliation.[269]

Toxic Shock Syndrome

Epidemiology. In addition to producing a variety of furuncles, abscesses, and bullous lesions, *Staphylococcus aureus* may also be responsible for scarlatiniform rashes that may manifest as a clinical syndrome indistinguishable from streptococcal scarlet fever, or as a multisystem disease associated with hypotensive shock and severe toxicity, called toxic shock syndrome. The rash often resembles that of scarlet fever, but hypotension, syncope, severe toxicity, myalgia, and vomiting and diarrhea may first bring the patient to medical attention. This condition is most common in menstruating women but has been reported even in infancy.[311] In a recent survey, the prevalence of toxic shock in Wisconsin was 6.2/100,000 menstruating women,[65] with women under 30 years two to three times more frequently affected than older subjects.

Pathogenesis/Etiology. *Staphylococcus aureus* strains that produce a toxin with pyrogenic and endotoxin-like properties are responsible.[278] These bacteria can be cultured from intravaginal tampons in many of these women,[235] although the condition has also been described in women using contraceptive diaphragms,[70] and in men after a variety of staphylococcal abscesses, with nasal or sinus packing,[306] bursitis, and other localized lesions, including surgical wound infections.[24] Newborns and young infants may also be affected.[255] Bacteremia is only occasionally present, as in a patient with staphylococcal endocarditis;[323] however, systemic absorption of toxin(s) is more important in the pathogenesis of the disease. Therefore, there are some similarities between this condition and staphylococcal scalded skin syndrome. Patients with toxic shock syndrome, however, are generally over 5 years of age and have cardiovascular, gastrointestinal, and renal components as major manifestations of their infection.

Clinical Manifestations. After an incubation period of approximately 2 days,[255] the patient may develop a variety of clinical manifestations (Table 7–16). Prominent are high fever, vomiting and diarrhea, abdominal pain, headache, chills, conjunctivitis, and a distinctive scarlatiniform, sometimes referred to as a "sunburn-like" rash. Other symptoms include confusion, orthostatic hypotension, syncope, and severe myalgia and malaise.[66] Several laboratory abnormalities reflect multiorgan dysfunction (due to the effects of toxin or shock, or both) and may be extremely diverse. These include hypoglycemia, hypocalcemia, hypophosphatemia, hypocholesterolemia, hyponatremia, hypoferremia, and lymphopenia. Not all patients meet these criteria, especially if treatment is begun early.[26] In such cases, orthostatic hypotension may not be present and multisystemic organ involvement may be minimal.

Diagnosis. The diagnosis is based on the presence of staphylococcal lesions or the use of tampons in a menstruating woman, associated with a sunburn-like rash and the onset of diarrhea, vomiting, weakness, myal-

TABLE 7–16. Toxic Shock Syndrome: Diagnostic Criteria

- Fever, usually > 39.8°C
- Scarlatiniform rash followed by desquamation (especially palms and soles 2–3 weeks later)
- Hypotension
- Multiple organ involvement
  - Kidneys
  - Liver
  - Central nervous system
  - Lungs
- Diarrhea
- Myalgia

gia, and systemic toxicity. Hypotension, oliguria, and other signs of multisystem involvement appear later. In some hosts, there may be no identifiable site of infection and the organism may be present only in the nasopharynx or other mucosal site. Although the diagnosis is based chiefly on clinical signs, adequate care must be taken in ruling out other possible diagnoses, such as streptococcal scarlet fever, staphylococcal and other causes of bacteremia, scalded skin syndrome, toxic epidermal necrolysis, severe erythema multiforme, leptospirosis, drug reactions,[35] and typical and atypical measles. Many of the laboratory signs associated with toxic shock syndrome are nonspecific but reflect organ damage, such as abnormalities in liver function, and azotemia and other secondary effects of shock. Among these are high serum creatine phosphokinase concentrations, as well as elevated serum concentrations of tissue transaminases and lactic acid dehydrogenase.

Therapy. Early treatment is critical in obviating many of the secondary effects of shock and toxic injury. If the patient is in shock, treatment of this must take first priority. Thus, adequate fluid and colloid replacement, careful attention to ventilatory and cardiovascular support, and use of dopamine should be considered. Antistaphylococcal antibiotics are important, but will have no effect on shock in the acute stages. Removal of tampons and contraceptive devices and adequate drainage of any foci of staphylococcal infection are mandatory. Although vaginal irrigation with sterile saline can be used to enhance drainage of lesions, topical antibiotics or disinfectants are generally not required. Parenteral antistaphylococcal drugs such as intravenous nafcillin or oxacillin should be prescribed. Cephalothin may also be used. Less ill patients, and those in convalescence, can be treated with oral dicloxacillin 75 mg/kg/day in four divided doses. Antibiotic treatment should be continued for approximately 5 days after the resolution of most of the clinical signs. Patients with renal failure may require dialysis and other supportive care.

Prognosis/Complications. Mortality rates as high as 20% were originally described in clinical experiences with this syndrome. With earlier diagnosis and aggressive management of shock, the prognosis is much better. However, sequelae may include vocal cord paralysis, impaired finger sensation, recurrent infection, and hair and nail loss.[55] Thus, this syndrome represents a major systemic insult, probably related to the elaboration of a single or multiple toxins and the capacity of these toxins to cause tissue injury in almost every organ in the body. Early recognition of Staphylococcus infection, particularly in high-risk individuals, such as patients with wounds and menstruating women, should reduce the severity of the illness and improve the prognosis. It is likely that many cases previously referred to as gram-negative sepsis, acute pyelonephritis, pelvic inflammatory diseases with septicemia and shock, etc., were really *S. aureus*-induced toxic shock syndromes.

Prevention. Neither toxic shock syndrome nor staphylococcal scalded skin syndrome is a preventable disease in the classic sense. That is, nosocomial infections and outbreaks of both conditions are not reported. However, it should be remembered that bullous impetigo may spread among nursery contacts and in closed populations.[192] Some hosts may manifest their disease as one of the more systemic syndromes mentioned above. Nonetheless, the mainstay for prevention is personal hygiene, early diagnosis, drainage, and appropriate therapy for localized staphylococcal infections. Washing of hands and wearing gowns are adequate measures of isolating these patients in hospital.

Scarlet Fever

Pathogenesis. Scarlet fever can be seen in association with streptococcal impetigo, wound infection, and, occasionally, with streptococcal pharyngitis, with or without exudative tonsillitis. Generalized rash and systemic signs are both a reaction to erythrogenic toxins produced by group A *Streptococcus pyogenes,* and also due to host hypersensitivity to these toxins. The differential diagnosis includes staphylococcal scarlet fever, toxic shock syndrome, mucocutaneous lymph node syndrome, hypersensitivity reactions, sunburn, acrodynia, and *Yersinia pseudotuberculosis* infection.[178]

Clinical Manifestations. After an incubation period of 1–3 days, a bright red flush appears on the face, followed by a red confluent rash over the trunk. This rash fades on pressure, although, in some areas, this is associated with petechiae. These are most prominent in the folds of joints (Pastia lines). The rash takes on a follicular raised appearance in some patients, particularly black subjects. The patient is usually febrile and may be toxic and anorectic. An enanthem is present in many cases which may include palatal and mucosal petechiae. The tongue is often involved as well, having a swollen, red, and mottled appearance. The furred hypertrophic mucosal surface of the tongue may peel, leaving prominent red papillae, often referred to as strawberry tongue. Rarely, jaundice and other signs of hepatitis may be present in the acute stages.[174]

Diagnosis/Treatment. Scarlet fever and its toxic fulminant form are now rarely seen in industrialized countries, presumably as a result of more effective antibiotic therapy, although epidemiologic shifts in bacterial prevalence and virulence may also be responsible. A throat culture is usually positive for group A Streptococcus and, rarely, blood cultures may also yield this organism. Serologic evidence of infection is manifest by rises in antistreptococcal antibody titers, particularly antistreptolysin O; however, these laboratory tests are rarely required to make the diagnosis. As for other streptococcal illness, the treatment of choice is penicillin for 10 days. Erythromycin or cephalosporins can be used for penicillin-allergic patients. A fine desquamation is frequently seen 1–10 weeks after the acute stage, which usually lasts approximately 1 week.

Complications/Prevention. Acute suppurative complications are rare in normal hosts; however, nonsuppurative sequelae, such as glomerulonephritis and rheumatic fever, may be seen if antibiotic therapy is not instituted within the first 5–7 days of infection. Patients are not considered contagious after the first 24 h of appropriate antibiotic therapy. Contacts should be observed carefully and throat cultures obtained for group A *S. pyogenes* in those who are symptomatic. Those with positive culture and those with signs of scarlet fever (regardless of the culture results) should be treated. Immunity is incomplete, since at least three distinct toxins have been identified.[189]

Wound Infection

Etiology/Pathogenesis. The majority of wound infections are seen in the context of surgical conditions. These occur after trauma, including human and animal bites,[201] and after surgery, and are associated with burns and decubitus ulcers. Depending on the source of the wound (i.e., animal, soil, acquired in hospital, aquatic, etc.) and the location (extremities, perineal area, mucosa, etc.), the etiologic agents vary markedly. For example, human bites are often contaminated with normal oral flora, including aerobic and anaerobic streptococci, staphylococci, Bacteroides, and a variety of other anaerobes.[47] Sites of animal bites may also contain *Pasteurella multocida* and even *Blastomyces dermatitidis.*[120] In contrast, pilonidal cyst abscess,[42] or traumatic wounds of the skin and subcutaneous structures in the perineal region, will often be contaminated with enteric bacteria, including Enterobacteriaceae, *Bacteroides fragilis,* or *Haemophilus aphrophilus,*[324] which are more likely to be resistant to penicillin.

The amount of necrotic tissue, the duration of bypass in open-heart surgery, reoperation, excessive bleeding, and the delay between the acquisition of the wound and cleansing and suturing are critical components in the development of wound infection.[87] Finally, the skill of the surgeon, the extent of the injury, the duration of the surgical procedure, the use of appropriate antiseptic techniques, and perioperative antimicrobial prophylaxis need to be considered as well. Clustering of cases should stimulate epidemiologic investigations to uncover sources of contamination, as illustrated by a series of streptococcal wound infections traced to a vaginal carrier.[32] Thus, the pathogenesis of wound infections can be extremely complex and diagnosis and management must be individualized in most cases. In general, the smaller and cleaner the wound, and the more rapidly it is cleansed and debrided, the less likely that a wound infection will ensue.

When one adds host factors to all of the above, the need for a specific etiologic diagnosis becomes even more obvious. For example, immunocompromised patients may be infected with a wide variety of agents. When these infections are related to a surgical procedure, or acquired in hospital, the likelihood of an opportunistic pathogen increases. These are not exclusively bacterial in nature, as illustrated by fungi and atypical mycobacteria,[140] as well as nosocomial herpes simplex infections. Cutaneous tuberculosis may also present as a persistent draining wound.[303] The presence of crepitation due to gas in a wound may indicate the presence of *Clostridium perfringens*[239] or other gas-forming bacteria.[4] When there is associated toxicity, this is a grave medical emergency requiring rapid surgical debridement and antibiotic therapy.

Diagnosis. The gram-stained smear of wound drainage is a rapid, inexpensive way to evaluate the inflammatory response and microbiologic flora of the suspected wound infection. Aerobic and anaerobic bacterial cultures are indicated in most cases and fungal or viral cultures in others. Examples of the latter include Candida or herpes simplex wound infections. Although the use of quantitative methods in the diagnosis and serial evaluation of wound (especially burn wounds) infection is controversial,[330] it is often helpful.

Clinical Manifestations. Most wound infections are characterized by inflammatory reaction in and around the wound site, including swelling, erythema, tenderness, pain on movement and, often, purulent or serosanguinous discharge. Microscopic examination of this material will reveal neutrophils and, sometimes, the pathogenic bacteria. Cultures are useful in these situations, since the variety of pathogens is great. In some circumstances, bacteria causing the wound infection may cause systemic effects as well. This is illustrated by surgical scarlet fever, which can be due to either toxin-producing *Staphylococcus aureus* or to group A Streptococcus.

Burn infections may manifest as purulence and local tenderness, but the burn wound surface may also act as an entry point for a wide variety of pathogens, leading to septicemia and focal infections. When the invading pathogen is poorly localized, the only clinical manifestation may be prolonged fever.[201]

Treatment. The principles for the management of superficial[160] and deep wound infections[161] of the hand have recently been outlined in some detail. These can be applied to most other wound infections as well.

Thus, drainage and debridement, elevation and immobilization of the infected extremity, and use of antibiotics are all important. The latter should be considered as adjunctive to drainage and debridement of necrotic tissue in almost all cases, including burns.[237] The threat of bacteremia and focal infection needs to be kept in mind, particularly in patients with extensive wounds, burns, and those with abnormal host defense mechanisms. In general, it is preferable to leave wounds open and to avoid the introduction of foreign bodies, such as drains and sutures, when infection is present. This principle applies just as well to infections of bone as it does to cutaneous wound infections. Thus, healing by secondary intention, use of appropriate antibiotics, allowing the affected area to rest, and removal of pus are of most benefit. A combination of antibiotics, debridement, and hyperbaric oxygen is recommended for severe gangrene.[230]

Systemically administered antibiotics penetrate well into wounds[30] and burns.[245] Use of topical antibiotics, antiseptics, and irrigating solutions should be minimized in most cases. An exception is the topical treatment of hospitalized patients with burns.[188] Although it is obvious that peroxide will often act as a chemical debriding agent, as well as stimulate phagocytic activity of neutrophils, injury to normal cells and tissue and delayed wound healing may also occur. Topical antimicrobials may also enhance the development of microbial resistance[207] and, when used in ointment and dressing form, may impede drainage. Topical povidone-iodine is not associated with enhanced wound healing or decreased wound infection; moreover systemic absorption may lead to some toxicity.[263]

Animal bites also introduce the risk of rabies, *Pasteurella multocida* infection, and cat-scratch disease. Dog and cat bites are most common and often heavily contaminated.[201] Occasionally, septicemia may result in cancer patients.[300] Antibiotics, such as penicillin, may be useful in patients at high risk of infection or scarring. This includes many individuals with cat punctures and facial lacerations.

Prevention. The prevention of wound infections can be most consistently achieved by rapid cleansing and debriding of wounds. There is universal agreement that excellent surgical technique and the reduction in the injury-repair interval are most important. Knowledge of the likely bacterial pathogen, clinical assessment of the degree of injury, host competence, soiling of the wound, completeness of debridement, etc., are factors used in considering antibiotic therapy. Several controlled studies have led to revised recommendations for the prevention of wound infection in common superficial injuries (Table 7–17). For example, in one study 265 patients with hand lacerations were randomly allocated to receive cephalexin, cefazolin, or placebo.[127] There was no difference in the wound infection rate. The same results were noted in a double-blind comparison of penicillin or placebo in dog bites[335] and in burns.[80]

TABLE 7-17. Prevention of Infection in Common Lacerations

Hand lacerations:	clean, no antibiotic[127]
Dog bites:	clean, no antibiotic[335]
Human bites:	dicloxacillin plus penicillin × 5 days[47]
Cat bites:	penicillin × 5 days

Wound infection associated with bowel surgery is more likely with operations on the colon, infected bowel (e.g., appendicitis), and in long complicated procedures with peritoneal soiling. In these situations, antibiotic prophylaxis is extremely useful.[289] Choosing drugs for surgical prophylaxis depends on the likely bacterial etiologies, as well as on the pharmacokinetic properties of the drug. Most drugs penetrate well into wounds, but some may be rapidly removed. This may explain the lack of efficacy of cephalothin in some wounds, as compared to cefazolin and cephaloradine.[244] Often several different antibiotic choices are justifiable. Those directed against anaerobes are helpful in bowel infection. For example, postappendectomy wound infections were reduced by 50% when metronidazole suppositories were used intrarectally beginning 40 min before operation and continuing for 2 days afterwards.[110] In the majority of cases, the most important rule is that antibiotics are adjunctive to the surgeon's skills and techniques, and are most effective when used immediately prior to the operation (i.e., within 1 h) by parenteral routes, and for no more than three or four postoperative doses. When wound infection is already established, continuation of antibiotics guided by appropriate cultures and in vitro susceptibility tests, and by knowledge of antibiotic activity, pharmacokinetics, and drug interactions will be useful for selecting appropriate regimens. In almost all such cases, adequate drainage of these wounds, removal of foreign bodies, and healing by secondary intention are of some importance.

Leprosy

Epidemiology/Etiology Leprosy (Hansen disease) is of major global significance, with an estimated 15 million people infected, mostly in tropical and subtropical regions.[104] The infection is due to *Mycobacterium leprae*, an obligate intracellular bacterial pathogen with an extremely slow generation time (approximately 12 days). Since the causative bacteria grow best at cooler surface temperatures, the macrophages in skin, and those surrounding cutaneous nerves (Schwann cells), are the usual targets.[36] The interplay of these infected macrophages and host cell-mediated immune responses are critical to the type of infection expressed clinically.[37]

Clinical Manifestations. After an incubation period of several years, single or multiple faint macules (hypopigmented in dark skin and erythematous in pale areas) begin to appear on the face or extremities, although all skin surfaces may be involved. It is estimated that 70% of these skin lesions heal spontaneously. The subsequent course of leprosy depends on the numbers of bacteria and, most importantly, on host cell-mediated immune responses (Table 7–18). Some patients present with the lepromatous form, although it is more common to see progression of disease from the indeterminate through the borderline form first. When lepromatous patients are first seen, they may present with one of the immune reactions to infection, such as fever, joint pain, arthritis, vasculitis, edema, nephritis, iritis, or erythema nodosum. These reactions may be extremely severe and some, such as vasculitis, may be due to dapsone therapy as well as to the disease. The clinical finding of anesthetic areas associated with skin lesions, in patients in or from warm climates, should suggest the diagnosis of leprosy.

Diagnosis. Confirmation of the diagnosis rests on visualization of acid-fast bacilli in skin biopsy or nasal blow smears. Skin may be obtained from the ear lobe or the dorsum of the finger by the slit or scrape techniques. The lepromin skin test is positive in the tuberculin form, but negative when cell-mediated immunity is absent. A recently devised ELISA serologic test may prove useful as well.[337]

Treatment. The mainstay of therapy for leprosy is dapsone. This drug is continued for 5 years for the tuberculoid form, 10 years for borderline forms, and for life with the lepromatous form. The emergence of resistance to dapsone is becoming a major problem.[190] Because of this, rifampin has been added to the treatment program for the first 3 years of therapy

TABLE 7–18. Clinical Classification of Leprosy

- Indeterminate
  - Macules
  - Immunity intact
- Tuberculoid
  - Few, well-defined skin lesions
  - Mononeuritis
  - Few bacteria in biopsy specimen
  - Lepromin skin test positive
  - Cell-mediated immunity intact
  - Not contagious
- Lepromatous
  - Systemic progressive disease
  - High bacterial count in lesions and nasal discharge
  - Lepromin skin test negative
  - Reduced or absent cell-mediated immune response
  - Contagious
- Borderline
  - Between tuberculoid and lepromatous
  - Skin test usually negative

in most cases.[333] Severe lepromatous cases should also be treated with clofazimine. The purpose of the rifampin and clofazimine therapy is both to serve as antibacterial agents and to prevent the development of drug resistance.

Dapsone reactions are occasionally seen after induction of therapy. They resemble infectious mononucleosis in many respects and may also include exfoliative dermatitis. These can be fatal.[112]

Prevention. This disease is most contagious in the lepromatous form, where respiratory and direct contact routes may play roles. It is also postulated that insect vectors may carry organisms from the skin of one patient to another in tropical areas. The contact required for spread is usually prolonged and intimate;[155] however, patients admitted to hospital with severe lepromatous leprosy should be strictly isolated until the diagnosis is confirmed and therapy initiated. Rifampin and dapsone rapidly render such patients noninfectious. The other forms of leprosy are rarely contagious. When a diagnosis of lepromatous leprosy is made, the spouse and household contacts under 10 years of age should receive 2 mg/kg/day of dapsone for 3 years as prophylaxis. Consideration of BCG vaccination should also be given for household contacts and for populations at high risk in endemic areas, although results of such vaccination programs have yielded variable benefits.[297] Successful growth of *Mycobacterium leprae* in armadilloes and primates has given new promise for the development of a specific vaccine.[204]

Leprosy is a disease that is frightening in its chronicity and expression, and baffling because of the precarious balance between the parasite and host responses.[37] Difficulty in management, isolation, and the complexities of therapy justify referral of such patients to specific treatment centers for diagnosis and initiation of therapy. In the United States, the National Hansen's Disease Center is located in Carville, Louisiana.

Pinta

Pinta is a treponemal skin infection due to *Treponema carateum*, seen predominantly in Central and South America. Lesions are confined to the skin and disease is transmissible by direct contact. Primary lesions are usually minor and consist of nodules or ulcers, easily confused with minor, traumatic abrasions. A secondary stage ensues 1–3 months after the indurated scaly primary lesions have usually disappeared. This is reminiscent of the secondary stage of syphilis in which widespread scaly, erythematous lesions involve most of the exposed areas of the skin. A late stage is characterized by the development of areas of skin depigmentation. Without treatment, this stage may be chronic or recurrent.

As with other treponemal diseases, the diagnosis rests on the typical clinical appearance, serologic tests for syphilis, and dark-field examination of fluid from the initial or secondary lesions. Penicillin therapy is effective.

Yaws

Yaws is a tropical skin disease due to treponemes and is seen mainly among rural populations in Africa, Southeast Asia, Australia, the Caribbean, and South America.[142] Recent increases in the incidence of yaws in Ghana have prompted the reintroduction of mobile treatment teams.[86]

The causative agent of yaws, *Treponema pertenue*, is introduced into areas of skin trauma and, after an incubation period of 3–5 weeks, nodular, papillomatous lesions develop. Although these may become depigmented and ulcerative, they generally heal. Several weeks to months later the secondary stage occurs, in which treponemes are disseminated to skin and other sites. Manifestations are mostly restricted to skin and bone, and include painful cutaneous palmar lesions that often weep a yellowish discharge. Bone involvement may be associated with pain and bony prominences of the face, head, and extremities. The third stage of yaws may not appear for 3 or more years. These lesions are painful and wart-like and are located on the hands and feet. They characteristically appear and disappear along with subcutaneous nodules. Scarring and depigmentation are common.

As with other treponemal diseases, serologic tests for syphilis are useful in diagnosis as dark-field examination of the primary lesions may be positive. Penicillin is effective therapy. Bejel, due to *Treponema pallidum* type II, is similar to pinta and yaws in its clinical expression, diagnosis, and treatment.

Fungal Skin Infections

Classification

The appearance of fungal infections of the skin is extremely variable and can easily be confused with a variety of infectious and noninfectious conditions. An example of the latter is pityriasis rosea, which may simulate tinea, secondary syphilis, and others.[52] Fungal skin infections are characterized by their chronicity and minimal inflammatory reaction, and can usually be diagnosed by relatively simple procedures. They are classified in terms of their location, e.g., tinea capitis, pedis (Fig. 7–18), faciei, corporis, unguium, and cruris,[153] or by the appearance of the lesions, e.g., ringworm (Fig. 7–19), tinea nigra, tinea versicolor (Fig. 7–20), and chromoblastomycosis. Yet a third classification is based on the causative

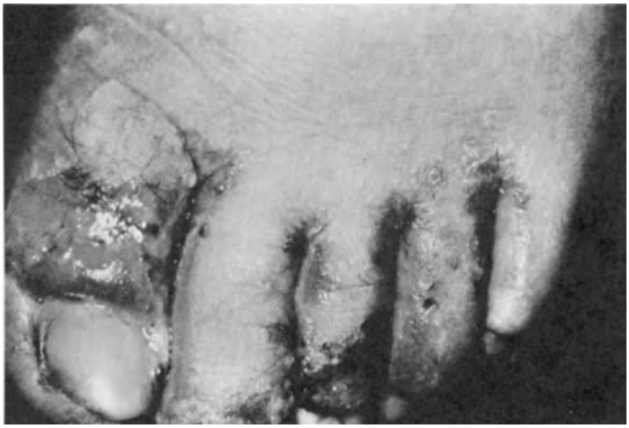


Figure 7–18. Tinea pedis.

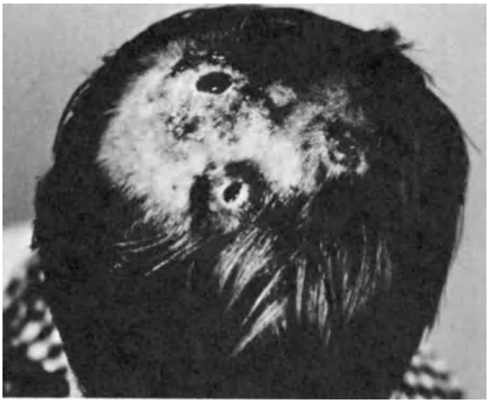
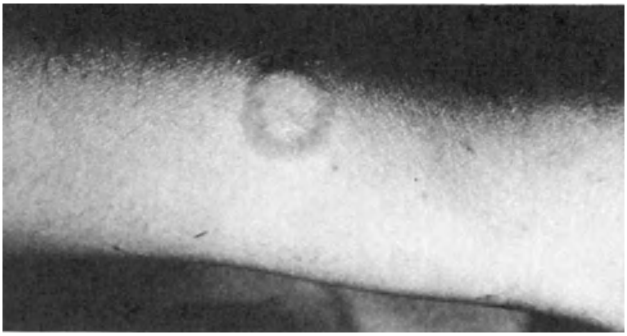


Figure 7–19. Ringworm. (Courtesy of Dr. H. Stutman.)



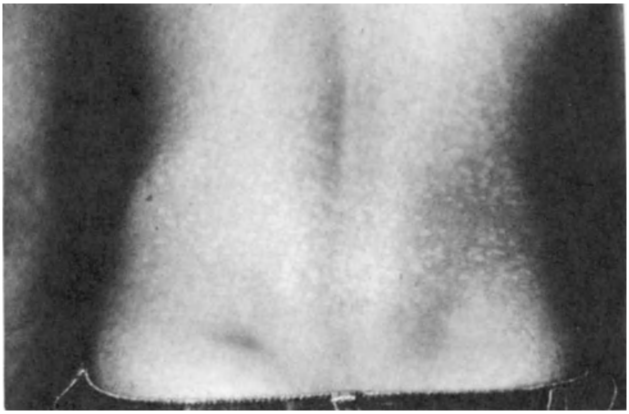


Figure 7-20. Tinea versicolor.

agent, e.g., trichophytosis, sporotrichosis, and phaeohyphomycosis. When the lesions are nodular or tumorous, they are sometimes called mycetoma or maduromycosis.[304] Although these classifications have created much confusion, knowledge of their derivation and intent should help. For the purposes of the practitioner, consideration of a fungal cause is most important, not the name given to the type or location of lesion.

Etiology

Several types of fungal skin infections can be defined.[91] The most frequently seen in North America consist of superficial skin, hair, and nail infections due to Trichophyton, Epidermophyton, or Microsporum (Table 7–19). Often, domestic animals are the reservoirs for Microsporum. These fungi cause ringworm or scaly, pruritic, and erythematous chronic skin lesions. When these lesions occur on the hands and are black, they are called tinea nigra and are usually due to (Exophialia Cladosporium). In skin folds, particularly in the perineal region, *Trichophyton rubrum* may be responsible, although in infants, *Candida albicans* is still the most common cause of skin infection at that site. The brown-colored (dematiaceous) fungi can also be responsible for these lesions.[49]

TABLE 7–19. Causes of Superficial Fungal Infections of Skin

Trichophyton
Epidermophyton
Microsporum
Exophialia (*Cladosporium wernecki*): Tinea nigra
Pityrosporum orbiculare: Tinea versicolor
Trichophyton rubrum: Tinea cruris
Dematiaceous fungi

Skin and subcutaneous lesions having a nodular appearance should suggest the possibility of sporotrichosis, particularly in warm climates, and when there is contact with outdoor plants, rose bushes, and moss. Nocardia, blastomyces, and dematiaceous fungi can also be responsible in these cases (Table 7–20). Rare imported causes should also be looked for.[5] The list of causative agents for all three categories of fungal infections grows to enormous lengths in tropical climates and in immunocompromised hosts. For example, cutaneous mucormycosis has been reported in infants with leukemia.[270] Animal contact and other occupational exposures may also increase the likelihood of acquiring bizarre fungal infections, particularly in traumatized areas.

When lesions become large and tumor-like in appearance, they are often called mycetoma (Table 7–21). These are most frequently seen in tropical climates and are of multiple etiologies. Occasionally, ringworm can take on this appearance when it becomes complicated by a pronounced allergic host inflammatory reaction, called kerion.

Clinical Manifestations. Erythematous, scaly, pigmented, pruritic lesions can be seen with a variety of superficial fungal infections.[91] Moist, warm, and dark body sites are particularly likely to be affected. When fungal infections involve the lymphatics, they often produce nodules in a linear fashion, such as seen in sporotrichosis. In hairy regions, alopecia is common. This, in fact, may be the only sign of ringworm of the scalp.[186] When nails are involved, they may take on a stained, crumpled appearance and may not grow well.[49]

Diagnosis. The diagnosis of superficial fungal infections is facilitated by direct observation of hyphal elements in scrapings from skin and nails. Ten percent KOH is used to break down the keratin and other background debris in these specimens. Occasionally, Wood's lamp may show fluorescence over areas of superficial skin fungal infections as well. When examining and culturing hairs, it is most important to include the hair follicle, since the fungal elements are usually located at that end. Culture of hair, skin, and nails on appropriate media (often selective for fungi by inclusion of appropriate antibiotics) will confirm the specific etiologic diagnosis. This should be carried out in most cases, since resistance to

TABLE 7–20. Nodular Fungal Infections

Sporotrichosis
Candida infections
Nocardia infections
Blastomycosis
Dermatophilus congolensis infections
Dematiaceous fungal infections

TABLE 7-21. Mycetoma (Maduramycosis)

Madurella mycetomatis
Actinomyces
Nocardia
Petriellidium boydii
Dematiaceous fungi

therapy, chronicity, and drug toxicities may require specific alterations in antifungal chemotherapy.

Therapy. The treatment of superficial fungal infections depends on the size and location. In small, well-localized lesions, topical antifungals such as tolnaftate, miconazole, clotrimazole, or nystatin (Chapter 2) should be tried first. If this is not successful after a 3- or 4-week trial, one of the systemic antifungals, griseofulvin or ketoconazole, is usually required.

In general, griseofulvin and ketoconazole are equally effective when used for the treatment of superficial skin infections.[119] In most of these situations, itching is reduced within a few days, and there is significant improvement in the local lesion within 2 weeks. Tinea capitis usually heals in 3–6 weeks.[186] These treatments should usually be continued for at least 6 weeks, and may be needed for 6 months or longer with nail infections. Scalp lesions are sterilized more quickly when 2% selenium sulfide shampoo is used twice weekly.[6] Ketoconazole has shown promising results in the treatment of tinea versicolor.[95] Monthly monitoring of the white blood cell count and liver function are necessary in the case of griseofulvin and ketoconazole, respectively.

In situations where response to therapy is slow, with the exception of tinea, surgical debridement may be necessary. This is particularly relevant for mycetoma. The treatment for sporotrichosis is different and requires potassium iodide (KI) (see Sporotrichosis below). Systemic antifungal therapy may be necessary in resistant cases, in immunocompromised hosts, and in progressive skin infections that may disseminate to other body sites. In vitro susceptibility data should be sought, and used to guide drug selection if initial antifungal therapy with amphotericin B or ketoconazole is unsuccessful. In specific circumstances, combinations of antimicrobials including ketoconazole or flucytosine may be required. Occasionally, therapy is not effective and the fungal infection must run its natural course. This may take a few months in skin locations, or a few years with nail involvement.[49]

Complications. Dissemination to extracutaneous sites may be seen with the dematiaceous fungi, as well as nocardia, sporothrix, and several of the other opportunistic infections. This depends on host characteristics including nutrition, the size and location of the lesion, and response to antifungal treatments.

Another complication of superficial fungal infections is kerion, a heaped-up suppurative inflammatory response to ringworm, particularly in hairy areas.[186] This type of lesion usually reflects an allergic response, although the appearance resembles a true abscess. The treatment of choice is the use of griseofulvin and systemic adrenal corticosteroids.[159] When used together, relief is often dramatic within 2 weeks, and resolution may be complete within 6–12 weeks. Incision and drainage, and antibiotics should be avoided, since these attempts will usually increase morbidity and not improve the course of this complication.

The vast majority of superficial fungal infections are benign and self-limiting, although chronic in nature. The chief morbidity associated with these infections includes cosmetic effects, irritation, and, in certain hosts, dissemination to extracutaneous sites.

Candida Skin Infections

Epidemiology/Pathogenesis. Candida species colonize the skin and gastrointestinal tract of approximately 30% of normal infants and children. The frequency of such colonization increases to approximately 65% by the third day of hospitalization.[203] Cutaneous candidiasis requires special emphasis because of its frequency, and its association with both disseminated disease and immunodeficiency states. Some of these manifestations in the newborn are discussed in Chapter 3.

Several species of Candida may be recovered from skin lesions, particularly in immunocompromised hosts; *Candida albicans* is most prevalent. Beyond the newborn period, antibiotics, diaper dermatitis, and various immune deficiencies are the most frequent predisposing factors. In older hosts, pregnancy, diabetes mellitus, oral contraceptives, and sexual transmission may be involved. Patients with skin diseases, such as eczema and seborrheic dermatitis, are more prone to skin colonization with Candida.[29] This is also true of patients with burns, in whom the risk of dissemination is related to the extent and degree of thermal insult and their immune competence.[187] Of increasing importance is the recognition of persistent Candida mucocutaneous infection in patients with underlying immune deficits,[60] including the acquired immunodeficiency syndrome.[318]

Clinical Manifestations. Maculopapular, erythematous lesions are most characteristic of Candida skin infection. Small satellite papules are often present, particularly in the diaper area (Fig. 7–21). Nevertheless, diaper area infections due to staphylococci, contact dermatitis, and superficial dermatophytes (Fig. 7–22) may be clinically indistinguishable from cu-

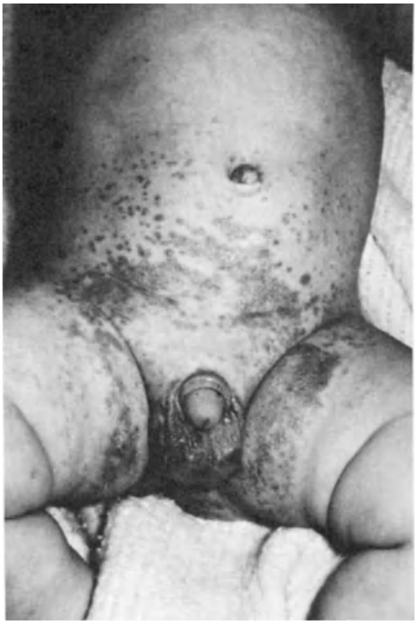


Fig. 7–21.

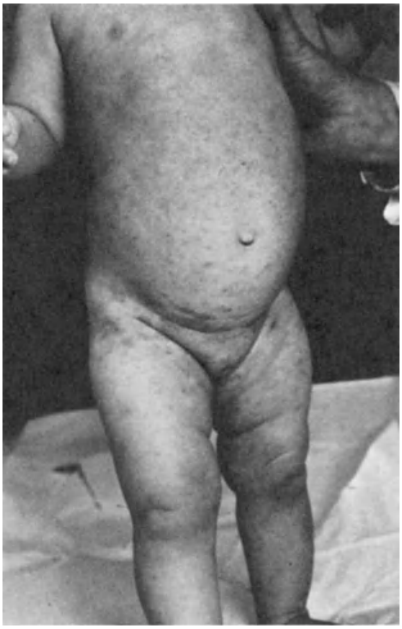


Fig. 7–22.

Figure 7–21. Candida diaper dermatitis.

Figure 7–22. Dermatitis due to *Epidermophyton floccosum*. (Courtesy of Dr. B. Brann.) For color reproduction of this figure see frontmatter.

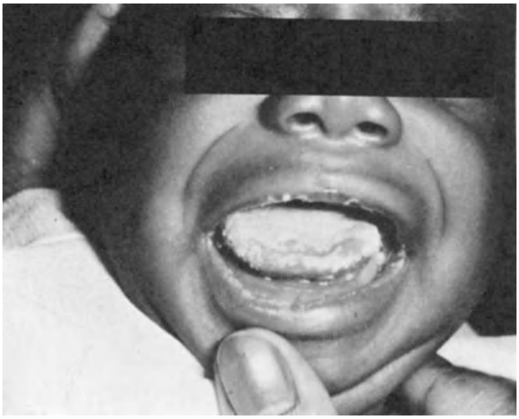


Figure 7–23. Oral candidiasis (thrush) in patient receiving antibiotics.

taneous candidiasis.[59] Moist areas of the skin, such as the axilla and perineal regions, are most commonly involved. Oral (Fig. 7–23), perioral, and perigenital skin lesions are common in patients receiving antibiotic therapy.

Cutaneous candidiasis is of particular concern in immunocompromised patients. When fever, skin rash, and muscle tenderness develop in such patients, the presence of Candida myositis and the potential for dissemination should be recognized.[152] Rarely, skin lesions may resemble ecthyma gangrenosum, usually the hallmark of *Pseudomonas aeruginosa* septicemia.[103]

Diagnosis. The diagnosis of diaper dermatitis due to *Candida albicans* is usually not difficult and can be made on clinical grounds, particularly in patients with oral or vaginal lesions who are receiving antibiotics. When doubt exists, or in the case of persistent lesions despite appropriate management, a rapid diagnosis can be made by KOH examination of skin scrapings. Culture is also readily positive and confirms the diagnosis. Muscle and skin biopsies can be used diagnostically in patients with burns and in those suspected to have more invasive infection.[177] Other diagnostic techniques are indicated when systemic infection is suspected (Chapter 12).

Treatment. When normal hosts acquire candidiasis, the first line of management should consist of an attempt to discontinue antibiotics or other predisposing factors. These may include intravenous catheters and nutritional or hygienic factors. Topical applications of nystatin, clotrimazole, miconazole, or amphotericin are all effective adjuncts. It seems unnecessary to use both oral and topical nystatin for the treatment of Candida diaper dermatitis.[222] Creams or lotions are probably more appropriate for use in intertriginous areas, whereas powders may be used on diaper rashes and for foot lesions. Where cutaneous lesions may be due to either Candida or superficial dermatophytes, clotrimazole or miconazole may be preferred, because of their broader antifungal action.

Mucocutaneous Candidiasis

Pathogenesis. Persistent skin or mucosal lesions due to *Candida albicans* should suggest the possibility of host immune deficiency. A variety of such deficiencies have been noted in patients with chronic mucocutaneous candidiasis, including decreased cell-mediated immunity, dysfunctional complement, phagocytic abnormalities, and defects in humoral immunity.[83] The disease may be classified into various subgroups based on the immunologic deficits described.[264] Occasionally, this syndrome is seen in families, where some members may progressively lose their cutaneous and cell-mediated immune responses to Candida.[273]

Clinical Manifestations. Patients with chronic mucocutaneous candidiasis have persistent and chronic infection of mucous membranes of the mouth and genital areas as well as the skin and nails (Fig. 7–24). Lesions of the angles of the mouth and paronychia are common, as is Candida esophagitis. The latter may be associated with laryngitis as well.[77] These lesions are extremely unresponsive to topical antifungal therapy.

Diagnosis. Demonstration of specific immune defects in patients with resistant and chronic mucocutaneous candidiasis confirms the diagnosis, but is possible in only 60–70% of patients at the time of initial presentation. Fungal cultures should be obtained in all such patients, since management will depend partly on in vitro susceptibilities and exact microbiologic confirmation of the diagnosis.

Therapy. A variety of therapeutic modalities have been used to treat the fungal infection and in an attempt to modify host immunity. Such modification, however, has generally been unsuccessful, although current attempts to reconstitute the immune system by bone marrow transplantation have been encouraging in some patients. A controlled study of transfer factor has yielded disappointing results.[217]

Ketoconazole administered orally once daily, on a continuous basis, seems the most efficacious method of controlling Candida infection in these patients.[267] Topical clotrimazole may also be a useful adjunct for the control of cutaneous[238] and oral[199] lesions. Some investigators have had success with intermittently administered oral clotrimazole as well.[262] These other modalities should be kept in mind, since therapeutic failures, recurrences, and the development of toxicity or resistance to ketoconazole

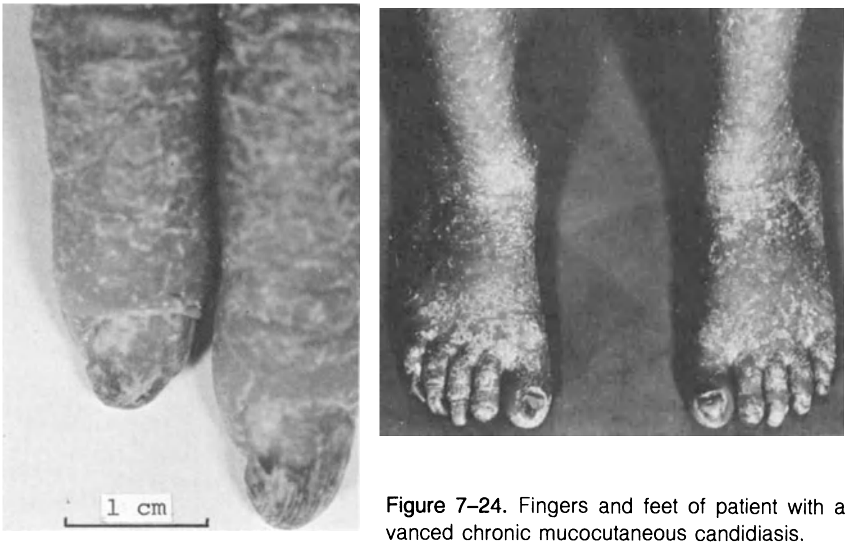


Figure 7–24. Fingers and feet of patient with advanced chronic mucocutaneous candidiasis.

are pitfalls of therapy in this chronic condition.[145] It appears that antifungal therapy must be continually maintained, pending immunologic reconstitution. In some patients, minimal doses can be used, obviating some of the dose-related toxicities noted with ketoconazole.

Complications. Chronic mucocutaneous candidiasis has been associated with myositis and thymoma in some patients.[173] Pernicious anemia, glomerulonephritis, invasive fungal infections (e.g., cryptococcosis, histoplasmosis),[168] and endocrinopathies have also been noted. The latter include hyperparathyroidism, Addison disease, and hypothyroidism.[12] It will be interesting to see whether such complications ensue despite effective control of the Candida infections. They may, in fact, become more prevalent, since the life span of these patients should be prolonged. Avoidance of such complications may depend on adequate immunologic reconstitution.

Sporotrichosis

Sporotrichosis is an uncommon cause of skin infection, but one that deserves emphasis because its treatment is markedly different from that used for bacterial and other fungal skin infections. Moreover, the lesions are easily confused with other nodular and pustular skin infections. Pulmonary manifestations of sporotrichosis are discussed in Chapter 5.

Epidemiology/Pathogenesis. Sporotrichosis is most commonly seen in warmer climates and in individuals exposed to garden plants, particularly rose bushes, sphagnum moss, and their products.[2] The fungus is accidently implanted into the skin and leads to chronic cutaneous and lymphatic lesions. In situations of malnutrition and other states of immunosuppression, a variety of extracutaneous manifestations are seen, including (rarely) fatal meningitis.[93]

Clinical Manifestations. The most classic manifestations of sporotrichosis are nodular cutaneous and subcutaneous lesions of the extremities, especially the hands and forearms. These are mildly tender, sometimes fluctuant, and red and swollen (Fig. 7–25). They usually follow the lymphatics in a linear fashion and the adjacent lymph nodes may be involved. Hence, the epitrochlear and axillary nodes are often enlarged. Initially, many of these lesions are mistaken for staphylococcal skin abscesses and are treated with antistaphylococcal antibiotics and, occasionally, drainage. Healing does not ensue and a variety of misadventures in management are often seen before the correct diagnosis is made. In children, lesions of the face and trunk are often noted.[197] In fact, these lesions may occasionally be confused with ringworm or facial cellulitis.[241] In certain hosts, particularly those who are immunosuppressed, extracutaneous in-

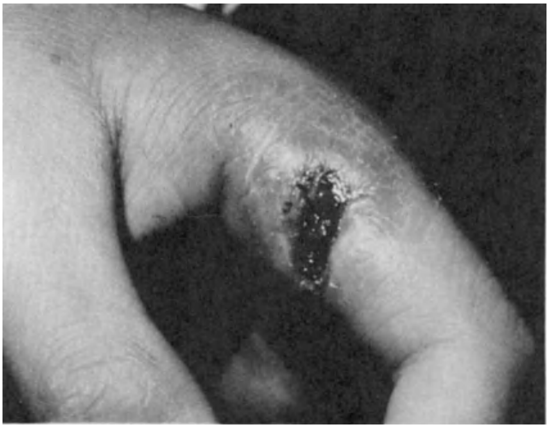


Figure 7-25. Sporotrichosis.

volvement may include lungs, central nervous system, bones, and joints,[61] and polytenosynovitis.[15]

Diagnosis. The diagnosis is usually made by a history of exposure to garden plants or moss, and the typical linear nodular lesions that have been present for several weeks to months. Gram stain may show a mixture of polymorphonuclear and mononuclear cells, and no bacteria. Bacterial cultures may contain *Staphylococcus epidermidis* or, occasionally, *Staphylococcus aureus* in small numbers. The KOH smear may show short cigar-shaped fungal elements but is usually negative. Careful culture techniques using selective enriched fungal agar will usually grow the organism. Serologic diagnosis can be made by the ELISA technique. In general, patients with extracutaneous involvement have higher titers than those with only skin, subcutaneous, or lymphatic infection. The differential diagnosis in many of these cases includes atypical mycobacterial disease, especially *Mycobacterium marinum* infection, *Nocardia brasiliensis* infection, tuberculosis, syphilis, tularemia, North American leishmaniasis, and cutaneous fungal infections, including those due to the agents of superficial and deep mycoses.

Therapy. Although spontaneous cure has been described,[22] the majority of these patients suffer from chronic, sometimes weeping, painful nodules. Therapeutic efforts may increase morbidity, especially after attempts at incision and drainage. Saturated solution of KI is considered the treatment of choice, and is usually administered orally by means of drops given three times a day until approximately a month after healing has occurred. It is wise to begin with a small dose (e.g., 10 drops/day) and increase the amount until either 150 drops/day are being used or the taste and gastrointestinal upset associated with this treatment preclude further increases in dosage. One should be alert to the risk of iodism and gastrointestinal disturbance. The former is suggested if the patient develops acneiform rash, excessive lacrimation, or swollen salivary glands. Preliminary experience with ketoconazole indicates that this oral antifungal drug has some suppressive effect but is not curative in this condition. Extracutaneous sporotrichosis should be treated with KI, although amphotericin B may be required as well. Complete eradication of sporotrichosis depends on competent host defenses. Antifungal therapy is far from satisfactory. Fortunately, the vast majority of infections due to this fungus involve superficial tissues and are readily eradicated with time.

Miscellaneous Causes of Skin Infection

The list of cutaneous manifestations of various infectious microorganisms and ectoparasites, such as scorpions,[257] is long. These lesions reflect direct tissue injury, inflammation, and nonspecific hypersensitivity reactions. Hence, these patients may manifest urticaria, pruritic erythematous rashes, or even erythema multiforme reactions associated with local and systemic infections. For example, tuberculosis may rarely manifest as reddish skin plaques, sometimes called "lupus vulgaris." Atypical mycobacteria (especially *M. marinum*) skin infections may result from aquatic exposure to salt-water fish. Lichenoid lesions and cold abscesses, as well as indurated vasculitis-associated lesions may also be seen with classic and atypical mycobacterial infections.[45]

Some cutaneous expressions of protozoan and helminthic infections are listed in Table 7–22. Of these, leishmaniasis is discussed in this chapter, toxoplasmosis in reference to newborns (Chapter 3), and schistosomiasis in reference to hepatic infection (Chapter 6). The reader is also referred to the chapter on genitourinary infections for discussion of cutaneous manifestations of sexually transmitted diseases, and to more detailed texts of parasitic and protozoal infections for specific features of some of the less frequently encountered infections.

TABLE 7–22. Examples of Protozoan and Parasitic Skin Lesions

Pathogen	*Skin Lesions*
Toxoplasma	Maculopapules
Leishmania (see text)	Nodules, ulcers
Trypanosomes	Erythema multiforme
Schistosoma	Pruritic, papulosvesicles
Onchocerca	Scaly papules
Taenia (cysticercosis)	Subcutaneous cysts
Filiaria	Edema
Dracunculus	Papule → ulcer → worm ± cellulitis

Acne vulgaris is not primarily infectious in its pathogenesis; however, *Propionibacterium acnes* and staphylococci are often present in the skin lesions. Oral tetracycline and topical erythromycin or clindamycin are effective in the management of moderate and severe cases. Their use is reviewed by Eady et al.[81]

Rocky Mountain Spotted Fever

Epidemiology/Pathogenesis. More than 90% of human rickettsial diseases in the United States are due to *Rickettsia rickettsiae,* the cause of Rocky Mountain spotted fever. The disease is most prevalent in the southeastern and south central United States, with most of the cases being reported from North Carolina, Virginia, Tennessee, Oklahoma, and South Carolina.[34] Thus, the name Rocky Mountain spotted fever is a misnomer, since < 5% of cases actually come from the Rocky Mountain states. Brill disease, murine typhus, Q fever, and rickettsial pox also occur in North America. Ticks, which inhabit woody areas in the spring and early summer months, are the major vectors, and man, an accidental host. Occasionally, cases are noted in winter as well.[183] Ticks are also a major reservoir for rickettsia, since they are passed transovarially from one generation to the next. The organisms may also be transiently present in small animals, including dogs, rabbits, etc.; these animals seem protected from the ill effects of this rickettsia, possibly due to acquisition of immunity from related, nonpathogenic microorganisms.

After several hours of tick attachment, the rickettsia are passed into the human host. Rickettsemia occurs (responsible for at least one case of Rocky Mountain spotted fever transmitted by blood transfusion),[321] followed by a diffuse vasculitis caused by infection of endothelial and vascular smooth muscle cells. Manifestations of disease are referable to this diffuse vasculitis in most instances.

Laboratory accidents have also resulted in human infection by aerosolization or by direct inoculation of rickettsia into skin abrasions. This can also occur by crushing infected ticks onto the skin.

Clinical Manifestations. Most clinical manifestations occur within 4–8 days after exposure to ticks, although symptoms may begin as early as 2, and as late as 14 days.[169] Fever, headache, and myalgia are prominent. There may be mild diarrhea, mild to severe abdominal pain,[64] chills, sore throat, nausea, and vomiting. A macular, maculopapular, and/or petechial rash is initially noted on the extremities, including the palms and soles (Fig. 7–26), and then spreads to the trunk. Although extremely rare, infection *without* rash has been noted.[322] Periorbital edema and mild conjunctivitis can also be present.

Other manifestations of Rocky Mountain spotted fever are diverse and nonspecific. These include evidence of hepatitis,[3] central nervous system involvement with stiff neck and laboratory signs of meningitis (CSF lym-

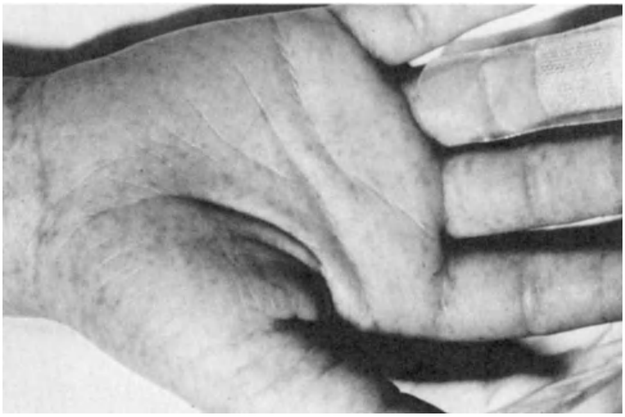


Figure 7–26. Palmar rash of Rocky Mountain spotted fever.

phocytic pleocytosis with a normal glucose, and a normal or a slightly raised protein concentration are the usual findings), myocarditis,[202] hepatitis, pneumonia,[74] and nephritis with hematuria and albuminuria. Other laboratory abnormalities include thrombocytopenia and hyponatremia.[164] Disseminated intravascular coagulation can occur in fulminant cases. The hyponatremia may be due to inappropriate antidiuretic hormone secretion when the central nervous system is involved or due to renal loss of sodium. Patients may have abnormal liver function tests [rises in serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase] that reflect hepatitis and/or vasculitis within the liver.[3]

Diagnosis. There is no simple rapid diagnostic test, although several investigators have suggested that fluorescent antibody demonstration of antigen in skin biopsies can be useful.[105] This requires special skills and equipment and is limited by cross-antigenicity with other organisms. Similarly, attempts to detect antigen in body fluids have yielded poor results. Antibody response to infection usually occurs after 14 days from the onset of illness, although occasionally rises can be seen as early as 5–7 days. Although rickettsia can be grown in yolk sac and recovered after experimental animal inoculation, these procedures are slow, and the hazards of working with rickettsia usually preclude this approach.

The latex agglutination test seems the most specific and accurate way of documenting antibody rises,[137] although complement-fixation and Proteus slide agglutination test can also be used. Because of cross-antigenicity between Proteus and these rickettsia, agglutination of Proteus OX19 in titers of 1/160 or greater can be used as a presumptive clue to the diagnosis of this disease in early specimens; seroconversion can be documented by a fourfold rise of antibody titer. Occasionally, Proteus OX2 agglutinins are also present in Rocky Mountain spotted fever.

The differential diagnosis of this disease centers primarily around the presence of a rash on the palms of the hands. Although this rash may be difficult to see in dark-skinned individuals, it is present in over 90% of cases. It can be enhanced by warm compresses or immersion of the hands in warm water. The diagnosis can be extremely difficult in the absence of rash but should be entertained seriously in patients exposed to ticks in endemic areas during the correct time of the year. Other causes of rashes of the palms and soles include drug hypersensitivity reactions and enteroviral infections (Table 7–23).

Treatment. The therapy of Rocky Mountain spotted fever should be started early, based on historical and clinical findings. Tetracycline 50 mg/kg/day or chloramphenicol 50–75 mg/kg/day should be used. Chloramphenicol is preferred for children under 8 years of age. The oral route is satisfactory for both drugs in those patients who are not vomiting. Therapy should be continued for approximately 5 days after the temperature has returned to normal, but at least for 7–10 days. Relapses can occur if therapy is shortened beyond this time, as both drugs are rickettsiostatic. Supportive therapy for the diverse manifestations of this infection may also be required. These may include hyponatremia, severe thrombocytopenia, myocarditis, meningoencephalitis, and the adult respiratory distress syndrome.[271]

Prognosis. Current mortality figures in North America for Rocky Mountain spotted fever are still around 5% for children. This can be improved by early diagnosis, although there appear to be some patients with a fulminant onset of neurologic and/or cardiac involvement who may have seizures and arrhythmias as early causes of death. The prognosis in those children who recover is excellent, although recent studies suggest there may be some permanent behavioral problems and learning disabilities in

TABLE 7–23. Differential Diagnosis of Rash Involving Palms and Soles

Meningococcemia
Drug hypersensitivity
Stevens-Johnson syndrome (erythema multiforme)
Enterovirus (especially coxsackie A)
Mucocutaneous lymph node syndrome (Kawasaki disease)
Atypical measles
Measles (rubeola)
Secondary syphilis
Rat bite fever[47]

patients who have a predominantly neurologic presentation; seizures do not seem to be a sequel to this disease, even though they may occur in the initial stages.[122] Other neurologic sequelae, such as neurogenic bladder,[144] may occur secondary to vasculitis and ischemia.

Prevention. At present, there is no licensed vaccine for the prevention of Rocky Mountain spotted fever, although there is one under investigation that may be reasonably pure and of low toxicity. Duration of immunity could be a problem with this type of killed vaccine. High-risk populations for consideration for vaccine include laboratory personnel working with rickettsia, forest rangers, and others who live and work in heavily tick-infested endemic areas.

Typhus/Rickettsialpox

Epidemiology/Etiology. Although much less common in North America than Rocky Mountain spotted fever, other, usually milder, rickettsial infections are occasionally seen, as illustrated by a recent outbreak of murine (endemic) typhus in Texas due to *Rickettsia typhi.*[108] The reservoir for this rickettsia is rats, and infection is spread to man by the rat flea. The flea bites through human skin and usually defecates at the same time. The resulting irritation leads to scratching and introduction of the rickettsia into the wound. Disruption of the rat population by construction or rodenticides often leads to human disease as the ectoparasite seeks new hosts.

Infection due to *Rickettsia prowazekii,* commonly called epidemic typhus, has also been described in the eastern United States. Here, the reservoir is the southern flying squirrel.[79] These diseases are more commonly seen in winter months, although recrudescent typhus (Brill-Zinsser disease) may be seen months to years after the initial infection.

Rickettsialpox is a mild infection due to *R. akari.* An eschar forms at the site of a mite bite and is followed by fever, headache, and a papulovesicular rash that rarely lasts more than a week.[41]

Clinical Manifestations. The rarity of diagnosed cases of typhus in North America probably reflects the nonspecific and self-limited nature of the infection, as well as several ecologic factors. Most cases are seen in young adults, although approximately one-third of cases may be seen in individuals under the age of 20. Two-thirds of patients have a macular rash that begins on the trunk and spreads to the extremities. Fever, headache, and myalgia are present, and the illness rarely lasts longer than 4 or 5 days. Deaths due to rickettsial infections other than Rocky Mountain spotted fever are extremely uncommon. Occasionally, typhus may be confused with Rocky Mountain spotted fever.[163]

Diagnosis. Typhus should be thought of in urban and rural populations, where rat populations have been considerably reduced, and in the eastern and mideastern United States, where a history of contact with flying squirrels is obtained. In such cases, the diagnosis is made by demonstration of a serologic response to typhus group rickettsial antigens as measured by complement-fixation or immunofluorescent antibody tests.

Treatment. Treatment of typhus and rickettsialpox is rarely required, since the disease is usually self-limited and diagnosed after the fact. If the disease is diagnosed in time, tetracycline or chloramphenicol are both effective. The disease is not communicable man-to-man except for epidemic typhus, which may spread in situations where lice infecting humans are present, since they may act as vectors. Vaccines are no longer available in North America because of the lack of demand and relatively low efficacy.

Leishmaniasis

Epidemiology/Pathology. Leishmaniasis is due to intracellular protozoa that reside predominantly in macrophages in the skin and throughout the reticuloendothelial system.[240] Rodents, sloths, dogs, and other mammals are the natural hosts. Leishmaniae are carried by sandflies to humans, where they enter through the skin.[181] Most of these infections are seen in the tropical and subtropical areas of the Eastern and Western hemispheres. The majority of cases in the United States have been observed in travelers to endemic areas.[251] Nevertheless, carriage in dogs has been demonstrated in both Oklahoma and Texas, and the potential for human disease is occasionally realized, although man-to-man transmission has not been demonstrated in North America. The impact of this infection globally is felt to be second only to that of malaria in numbers and morbidity. Expression of disease and its resolution are dependent on adequate host cell-mediated immunity.[240]

Etiology. Leishmaniasis is caused by protozoa of the genus Leishmania. At least seven species have been associated with cutaneous disease in man.[181] *Leishmania donovani* (*chagasi*) causes most cases of visceral leishmaniasis.

Clinical Manifestations. There are three clinical forms of leishmaniasis: cutaneous, mucocutaneous, and visceral. Skin lesions, referred to as "oriental sores," are the most frequent form. These are single or multiple lesions that usually occur on the face, arms, or legs 2–8 weeks after a sandfly bite.[198] The lesions begin as erythematous papules approximately 2–5 mm in diameter and gradually grow to 1–2 cm in size. Ulceration occurs within a few months, and healing with scarring generally within 2 years; however, more chronic cutaneous forms (as long as 30 years!) have been observed.

Mucocutaneous leishmaniasis is similar to cutaneous disease, except that it is characterized by more nodularity and ulceration, and by involvement of the mucous membranes of the nose and mouth. Ulcerations of bone and other subcutaneous tissue may lead to severe deformities.

Visceral leishmaniasis is often difficult to diagnose because of the nonspecific expression of the infection, such as prolonged fever.[117]

In the United States, patients usually report travel to endemic areas, but still present serious diagnostic problems, often solved only by laparotomy and examination of appropriate tissue biopsies. Fever in these cases generally exhibits a twice/day pattern and may be associated with dizziness, weakness, weight loss, and pancytopenia. Hepatosplenomegaly, anemia, and cutaneous lesions associated with widespread lymphadenopathy in patients who have travelled or lived in endemic areas should suggest this diagnosis. Diarrhea and malabsorption may be due to intestinal parasitization in some cases.[221]

Diagnosis. Confirmation of leishmaniasis depends on demonstration of Leishmania organisms within macrophages obtained from skin scrapings or from other infected tissues. Skin specimens should be obtained from nonulcerated lesions superficial to the dermis. Geimsa staining will often demonstrate Leishman-Donovan bodies, which are forms of the protozoan (amastigotes) seen within macrophages. Culture of appropriate skin or tissue specimens on diphasic blood agar at 22°C for 3 weeks, or inoculation into hamsters, may also provide the diagnosis.[198] In the latter instance, Leishman-Donovan bodies are seen in splenic tissue obtained from the hamsters approximately 2 weeks after inoculation.

Treatment. Therapy is a disappointment in this disease. Even when the diagnosis is made, treatment is often ineffective (especially in visceral infection), or only brings about a temporary remission. The cardiac and hepatic toxicities of sodium antimony gluconate are also problematic. This drug is used according to the schedule outlined in Table 7–24. Visceral leishmaniasis in Kenya has also responded to sodium stibogluconate 10 mg/kg every 8 h for 10 days, in a preliminary trial.[57] Amphotericin B has also been used, but with inconsistent results. Although encouraging results have been reported with metronidazole, subsequent study has not confirmed this impression.[320] Caution is also urged in interpreting recent reports of synergistic activity against leishmaniasis by a combination of rifampin and isoniazid,[242] and co-trimoxazole (TMP-SMZ).[223]

The ultimate solution for the world leishmaniasis problem will probably depend on the development of an effective vaccine. In the meantime,

TABLE 7-24. Dose of Sodium Antimony Gluconate for Treatment of Leishmaniasis[198]

Age	*Daily IV Dose (100 mg antimony/ml)*
14 years or older	6 ml
2–13 years	4 ml
Under 2 years	2 ml
Total number of injections=	
6 for Indian Visceral form	
10 for cutaneous old world form	
30 for others	

the scope of the natural reservoir and the ubiquity of the sandfly vector hamper effective control measures.

Filariasis/Onchocerciasis

Epidemiology/Etiology. Filariasis is widespread in West Africa and Central America, and it is estimated that 30 million persons are infected worldwide. The causative agent of onchocerciasis is a filarial parasite, *Onchocerca volvulus,* which is transmitted to man by black flies indigenous to these geographic areas.[124] Other filarial parasites of man include *Wuchereria bancrofti, Brugia malayi,* and *Loa loa.*[229] Once the adult forms in the skin of the patient (noted by the presence of a nodule), it begins to produce millions of eggs which mature into microfilaria that migrate throughout the host.

Clinical Manifestations. The skin and eyes are most frequently involved in onchocerciasis.[78] Lymphedema and fever are the major features of filariasis.[316] After inoculation of the adult filaria under the skin, localized pruritus and nodule formation are noted. An erythematous scaly rash supervenes and secondary infection due to scratching may occur. This is followed by the formation of subcutaneous nodules, particularly prominent over the thighs and buttocks. The nodules and overlying skin lesions may suggest the diagnosis of leprosy. When these are extensive, there is associated lymphadenopathy and the skin may take on a "crocodile-like" appearance. Widespread cutaneous involvement may be extremely debilitating. The West African eye worm, *Loa loa,* or onchoceriasis is often responsible for ocular inflammation. In several cases of onchoceriasis ocular involvement may lead to blindness. Earlier changes include decreased visual acuity due to the presence of iridocyclitis and/or keratitis. Chorioretinitis may also be noted.

Diagnosis. The diagnosis is most frequently made by demonstration of microfilaria in skin snips or shavings examined by light microscopy. Demonstration of filaria in peripheral blood smears (best obtained at midnight) is diagnostic.[229] Occasionally these can also be seen in superficial conjunctival tissues and urine. Peripheral eosinophilia often reaches 50% of the white blood cell count, although this is a nonspecific finding.

Treatment. The treatment of onchocerciasis is far from satisfactory. The filaria load may be extremely high and many of the signs and symptoms are due to host hypersensitivity responses. Although diethylcarbamazine has some activity, it is extremely toxic, as is suramin, the other conventional therapy for this condition. A prior single dose of levamisole 2.5 mg/kg may enhance the action of diethylcarbamazine.[310] Recent controlled trials have suggested that mebendazole, 1 g twice daily for 28 days,[258] or a single dose of ivermectin[18] may be useful. The latter, or flubendazole,[73] may revolutionalize the treatment of onchocerciasis and markedly reduce both the cutaneous and ocular morbidity associated with it. Prevention of the disease otherwise depends on vector control.[124]

Scabies

Etiology/Pathogenesis. Scabies is a result of skin infestation by the adult female ectoparasite, *Sarcoptes scabiei* var. *hominis.* Occasionally, scabies from puppies may infest humans as well. For approximately 3–4 weeks after infestation, there is little reaction in the human host. During this time, the adult female creates a burrow in the skin and lays her eggs.[286] The host develops hypersensitivity to the eggs, feces, and developing mites. It is this host reaction that is responsible for the symptoms of the disease. Evidence for hypersensitivity includes intense pruritus, the occasional appearance of urticaria, and the demonstration of IgE and IgG deposits in these skin lesions.[54]

Clinical Manifestations. There are several ways in which scabies may manifest. The most frequent form is characterized by erythematous papules, burrows, and nodules in the finger webs, elbow creases, axillae, and on the buttocks (Fig. 7–27). There is intense itching, especially at night. This may involve several family members in the same household.

Occasionally, patients with underlying immunocompromised conditions may have extensive crusted dermatoses with minimal pruritus, so-called "Norwegian scabies."[339] These patients are believed to have reduced cell-mediated immune responses to the adult and mite antigens, and have a considerably greater burden of parasites than patients with chronic scabies. The lesions are thick, crusted, and form plaques on the palms, soles, scalp, ears, and extensor surfaces of the extremities. A modified form of this condition is seen in newborns, in whom the diagnosis may be very difficult to make.

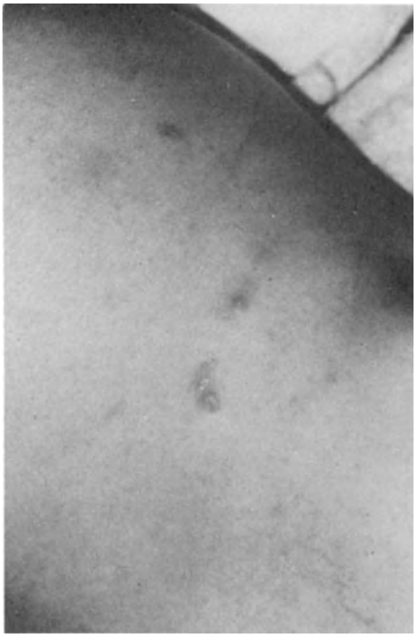


Figure 7–27. Scabies.

Other less common clinical manifestations of scabies include urticaria[54] and bullous lesions.[28]

Diagnosis. The diagnosis of scabies is suggested by the intense itching, the appearance of the skin lesions, and the coexistence of several cases in the same household. Confusion with other causes of urticarial and bullous diseases, and streptococcal cellulitis or other superinfecting conditions, is common. The chronicity of the condition and the pruritus are often useful differentiating characteristics. The diagnosis is confirmed by microscopic examination of a scraping of a burrow or nodular lesion. This is facilitated by application of mineral oil over the lesion and scraping with a scalpel blade. Sometimes, application of ink over a burrow will delineate the linear nature of the lesion and allow more precise sampling. Microscopic visualization of eggs, feces, or mites in skin scraping is diagnostic.[92] Skin biopsy is seldom required; however, it will often demonstrate mites, eggs, or feces within the stratum corneum of the skin.

Treatment. Lindane, 1%, is the recommended treatment for the patient and intimate contacts, which should include all household members and sexual partners.[92] This treatment is not recommended for patients under 2 years of age, since systemic absorption of this product may be toxic to younger patients. The lindane is applied once, left on overnight, and washed off in the morning. A careful single application is usually curative.

If there is any doubt about patient compliance, a second application is required. Remember, pruritus may persist up to a week after killing of all adult scabies and mites.

To avoid the central nervous system toxicity of lindane, crotamiton can be applied after a bath or shower. A repeat application is recommended after 24 h, and then a cleansing bath 48 h after both applications.

Five percent sulfur in petrolatum can be used in infants and is applied two to three times at 24-h intervals, followed by a cleansing bath 24 h later. This latter treatment is malodorous, but may be the only approach to the treatment of the disease in the newborn.

Prevention. Scabies requires direct contact for spread and is most contagious in patients with the Norwegian form, which has an extremely high mite load. In other cases, the disease is rarely transmitted by casual contact or through fomites. Nevertheless, careful personal hygiene and laundering are useful adjuncts in the treatment of this condition. Crowding, poor hygiene, malnutrition, and immunocompromised conditions favor development and chronicity of this infestation.

Pediculosis

Infestation with head lice is common in school-age children and may occur in large outbreaks. Crab lice (Phthirus pubis) may also be sexually transmitted. The head louse (*Pediculus humanus capitis*) is a blood-sucking ectoparasite that lays its eggs on hair shafts. Skin irritation and itching predominate clinically, and the diagnosis can usually be made by the observation of small nits tenaciously attached to hair shafts within 6 mm of the scalp. Any hairy part of the body can be infested. When eyelashes are involved, this is usually due to crab lice and there may be associated blepharitis or conjunctivitis.[172] In such cases, sexual abuse should be considered.

The body louse (*Pediculus humanus*) may serve as the vector for epidemic typhus, trench fever and louseborne relapsing fever.

Therapy. Gammabenzene hexachloride (lindane) has been the mainstay of therapy for pediculosis for years. One application usually suffices, although repeat treatment in a week's time may be necessary. Shampooing the affected area with a teaspoon or two of lotion is usually adequate. Some lice have developed resistance to this chemical, which has limited its usefulness in certain outbreaks. Moreover, systemic absorption can occur when lindane is used over large excoriated and inflamed surfaces, which can result in neurotoxic reactions and local irritation. Alternatives include pyrethrins, which are also applied as a shampoo (one or two applications separated by a week).[260] Pyrethrins may not be effective in killing ova; hence recurrence is possible. In such cases, 0.5% malathion lotion may be applied for a 12-h period and is highly effective.[307] Adjunctive therapy for the treatment of lice and interruption of transmission includes hot water laundering and hot drying of bed linens, disinfection of combs, and careful personal hygiene.

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8

Bone and Joint Infections

Osteomyelitis

The incidence of bone infections continues to be high and the clinical consequences serious.[98] This situation is due partly to nonspecific presentations, particularly in young patients. Most cases of osteomyelitis occur after hematogenous spread of bacteria or other microorganisms and involve the metaphyses of long bones, particularly those of the femur, tibia, and humerus, which account for approximately three-quarters of all cases. Any bone or joint space in the body can be involved, and cases of osteomyelitis epiphyses, of the vertebral bodies, disc space, and pelvis[38] are not uncommon.

Osteomyelitis after trauma or surgery is also an important source of morbidity, and can result in a diversity of bone, joint, and soft tissue infections of single or mixed causes that reflect the particular exposure. If the injury occurs in a soil environment, *Clostridium sp., Pseudomonas aeruginosa,* bacterial opportunists, and unusual fungi may infect bone. A rare, and often neglected, predisposing factor is septic thrombophlebitis, sometimes induced by the presence of intravenous catheters.[44]

Epidemiology

The incidence of osteomyelitis has remained relatively constant during the past decade, although the prognosis has steadily improved since the introduction of antibiotics. There is a slight preponderance in males and most cases are found in children between the ages of 1 and 12 years.[56] However, osteomyelitis in the newborn or osteomyelitis associated with an underlying disease, trauma, surgery, and decubitus or ischemic ulcers is not uncommon in individuals outside of these ages. The frequency of osteomyelitis reflects, in part, the amount of trauma to which the child is exposed and the characteristics of personal hygienic practices and environment. Frequent skin infections, for example, may predispose the individual to staphylococcal bacteremia with subsequent increased risks of hematogenous osteomyelitis.

Pathogenesis

The majority of children with acute osteomyelitis have bacteremia before localization of infection in the bone. The origin of bacteremia is often obscure, although skin lesions, respiratory, and, occasionally, gastrointestinal sources are sometimes evident. The initial lesion is usually present in the venous sinusoids of the metaphysis with subsequent spread of infection and inflammation. The term "acute" is usually reserved for infections that have not progressed farther than the subperiosteal space. Significant osteolysis, the development of sequestra, which represent pieces of necrotic bone, and surrounding new bone formation (involucrum) are hallmarks of chronic osteomyelitis. Occasionally, infection may be sequestered in a small walled-off abscess. This form of osteomyelitis is classified as subacute and is often called Brodie abscess.[54] Usually these sites are sterile when explored, but sometimes harbor Staphylococcus.

Osteomyelitis from contiguous sites of infection is also seen. An example is bone infection beneath decubitus ulcers.[94] Clinical suspicion of this complication is warranted in patients with poorly healing and deep pressure sores. Radiographs and radionuclide scans are helpful in the diagnosis, but bone biopsy is often required for histopathologic confirmation of the diagnosis and for preparation of accurate cultures. Anaerobic and mixed bacterial infections are often found to be the causes.

Etiology

Many factors influence the occurrence, etiology and course of osteomyelitis due to microorganisms. These include the age of the patient, underlying conditions, and the site of infection. Use of drugs, nutritional status, and genetic factors may be significant, as they have marked effects on the immune competency of the host.

Noninfectious. Before discussing the microbiologic causes, it would be worthwhile to consider the differential diagnosis of osteomyelitis. In young children, traumatic bone injury may be difficult to differentiate from osteomyelitis, as the history may be unreliable.

The diagnosis is also tricky in newborns, in whom cellulitis, due to infection or toxic drugs, may be difficult to differentiate from bone infection.[70]

Patients with sickle-cell disease may also present a dilemma in differential diagnosis, in consideration of the common findings of fever, bone pain, and malaise in this condition.[100] Occasionally trauma[67] and/or bone infarction[27] may coexist with osteomyelitis. Decreased uptake of technetium at the point of tenderness during the first few days of illness suggests infarction rather than infection in sickle-cell disease patients.[48] Similarly, a low neutrophil or band cell count is a diagnostic clue in favor of sickle-cell crisis and against infection.[10] Many patients present after the first day or two of signs, however, and require surgical exploration by needle or open biopsy to differentiate these two conditions. Since Salmonella osteomyelitis is a particular risk for these patients, blind therapy directed against Staphylococcus would be especially hazardous.[27]

Recurrent multifocal osteomyelitis may reflect posttraumatic fat necrosis or an idiopathic condition, characterized by pustular skin lesions and involvement of the clavicles. These patients have negative microbiologic findings, and may occasionally develop leukemia at a later date.[7] In summary, the differential diagnosis of osteomyelitis should include trauma, infarction, bone cyst, tumors (primary and metastatic neoplasms), lymphoma/leukemia, and multifocal idiopathic osteomyelitis.

Infectious. The microbiologic causes of osteomyelitis are diverse, but the majority of cases of acute hematogenous disease are due to *Staphylococcus aureus. S. epidermidis* is also important. *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*[74] are rare causes of osteomyelitis, despite the fact that they are frequent causes of bacteremia. In some cases, as cited above in reference to meningococcus, the bone lesion may represent infarction secondary to septic embolization or disseminated intravascular coagulation. When septic arthritis is associated with osteomyelitis of the adjacent bone, however, *H. influenzae* infection should be given more serious consideration in children under the age of 4 years, and gonococcus and tuberculosis in older subjects.[19] In newborns, group B Streptococcus and gram-negative bacteria are more frequent causes of osteomyelitis, although bone infection is not common in individuals of this age (Chapter 3).

There are some clinical clues that suggest other specific etiologies (Table 8–1). Malnutrition seems an important predisposing cause of anaerobic osteomyelitis, as is trauma to the sinuses, oral cavity, long bones, pelvis, and spine.[60] Unusual commensals may rarely be involved (e.g., Veillonella).[4] A striking association between puncture wounds of the foot (Fig. 8–1) and *Pseudomonas aeruginosa* infection has been noted frequently[53] although the source of the organism remains obscure.[25] More recent observations indicate that rubber soles of running shoes may harbor Pseudomonas. Rarely, atypical mycobacteria (especially *M. fortuitum*) may be present in such patients.[12] Puncture wounds caused by thorns[75] or sharp objects contaminated with oral secretions may result in periostitis or osteomyelitis due to *Enterobacter agglomerans* or *Eikenella corrodens*, respectively. In all cases, *S. aureus* must be given initial consideration as the cause of bone infection.

Patients with underlying conditions are prone to opportunistic invasion

TABLE 8–1. Clinical Features That Suggest Specific Causes of Osteomyelitis

Clinical Features	*Suggested Causes*
Newborn	*Streptococcus agalactiae* (group B) *Escherichia coli*
Sickle-cell disease	Salmonella Anaerobic bacteria
Puncture wound of foot	*Pseudomonas aeruginosa* Atypical mycobacteria
Malnutrition	Salmonella Anaerobic bacteria
Diabetes mellitus	Fungi: Candida Torulopsis Mucor
Rheumatoid arthritis	*S. aureus* (contiguous spread from joint) *Pasteurella multocida*
Drug addiction	*E. coli* *Pseudomonas aeruginosa* Serratia Fungi
Dog/cat bite	*P. multocida*
Human bite	Anaerobic bacteria
Decubitus ulcer	Anaerobic bacteria

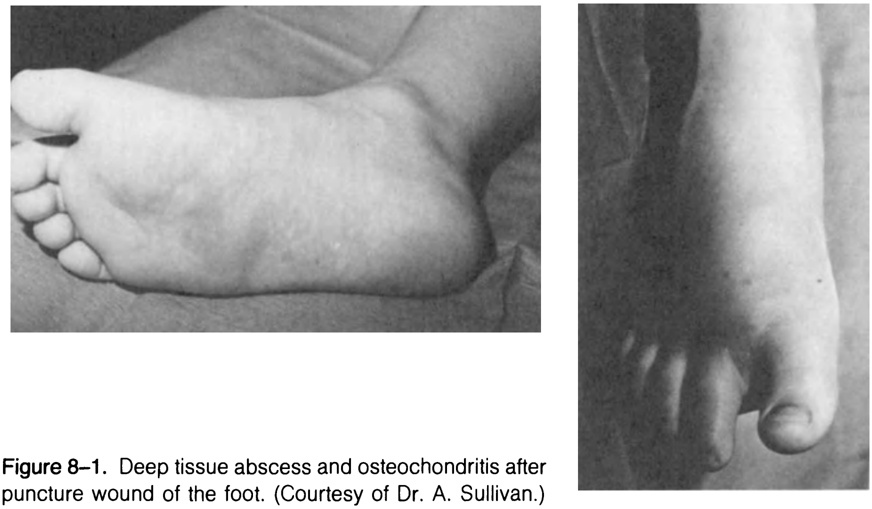

Figure 8–1. Deep tissue abscess and osteochondritis after puncture wound of the foot. (Courtesy of Dr. A. Sullivan.)

at many sites, including bone. Hence Neisseria,[16] Brucella, Pasteurella,[43] Moraxella,[93] *Streptococcus viridans,*[73] meningococcus,[3] *Mycobacterium tuberculosis*[84] and other mycobacteria, and fungi, including Candida, Histoplasma,[29] Coccidioides, Rhizopus,[17] Aspergillus[13], and Blastomyces, have been reported to cause bone infection. These infections, as well as polymicrobial osteomyelitis,[66] may reflect host and/or geographic factors.

Diagnosis

The child with fever, limp, and systemic toxicity rarely presents a major problem in diagnosis. The characteristics of local heat, redness, swelling, bone pain, and restriction of movement are classic. The pain is severe and is often unrelieved by rest or mild analgesics. The diagnosis may be less obvious in young infants, who may refuse to move an extremity or who may demonstrate an abnormal posture. Concomitant or prior respiratory or gastrointestinal infection, or trauma, may complicate the clinical diagnosis, as may other underlying diseases with manifestations that may mask the presentation of osteomyelitis. Similarly, the clinical features take on different characteristics when the condition is seen very early or late in its course. In the very early stages, the patient may present with signs of septicemia. Hence, chills, fever, malaise, nausea, vomiting, and headache may predominate. Bacteremia is often present and hypotension can occur. The classic signs of osteomyelitis may also be absent in the patient with subacute or chronic disease. In the former case, recurrent pain and the absence of systemic signs and symptoms are common. Chronic disease may be completely quiescent between periods of exacerbation. Only radiographs and/or bone scans may reveal the lesion at that time.

The physical examination of these children should include other joints and bones as well as skin, pulmonary, and cardiovascular sites where Staphylococcus can localize. These considerations should be kept in mind with regard to the laboratory diagnosis of osteomyelitis as well. The possibility of vertebral osteomyelitis or sacroiliac and pelvic infection warrants aggressive diagnostic procedures and intensive antibiotic therapy.[78] Gait abnormalities are present in most cases and *Staphylococcus aureus* is the usual cause. On occasion, the site of pelvic osteomyelitis may be obscured by gonadal shielding for radiographs or by pooling of radionuclide in bladder urine.[87] These patients are often misdiagnosed as having septic arthritis of the hip.[35]

Our first impulse when suspecting a diagnosis of bone infection is to obtain a radiograph (Fig. 8–2). This is good strategy; however, it should be remembered that bony changes might not ensue for 10–14 days (5 days in newborns) in the majority of cases. The acute hematogenous stage is, after all, a bacteremic illness and, therefore, blood cultures should be obtained. Since *Staphylococcus aureus* infects many organs, chest radi-

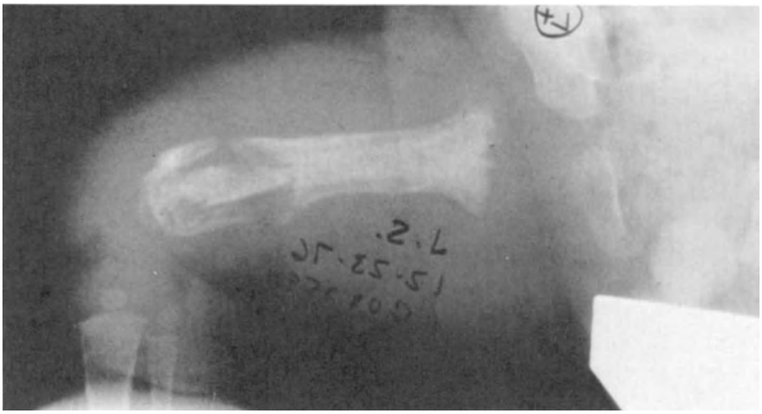

Figure 8–2. Radiographic appearance of advanced osteomyelitis. (Courtesy of Dr. A. Sullivan.)

ograph, urine culture, and smear and culture of skin lesions are also in order.

The most accurate means for establishing a diagnosis and defining the etiology of bone infection in cases advanced beyond the bacteremic phase is by culture of material aspirated directly from the subperiosteal space or bone. If pus has extended to the subperiosteal space, then gram stain and culture of this material will provide a diagnosis in more than 90% of instances. If bone changes are present radiographically, bone aspiration or biopsy material should be cultured and examined histopathologically. For example, the diagnosis of tuberculous osteomyelitis usually depends on the presence of a positive tuberculin test, positive acid-fast smears and/or cultures from joint fluid or bone lesions, and/or demonstration of caseous granulomas in bone biopsy material.[64] Sinus tract cultures are most reliable if they grow *S. aureus.*[49] In some cases needle aspiration will serve to differentiate cellulitis or subcutaneous abscess from osteomyelitis.

All cultures obtained in suspected cases of osteomyelitis should be processed in a careful manner. Since staphylococci may be causative, skin cutures should be taken of the prepared site before obtaining bone or blood culture specimens. The laboratory procedures used in the diagnosis of osteomyelitis are summarized in Table 8–2. It is recommended that two blood cultures be obtained in most cases. One should be done initially and the other after an invasive diagnostic procedure, since bacteria may be liberated into the bloodstream during needle aspiration. Blood cultures done immediately after this procedure may provide the etiologic diagnosis. Hypertonic media should be employed to culture specimens from patients who have already received cell-wall-active antibiotics. Similarly, procedures to remove antibiotics should be used in specimens of blood, joint fluid, and urine from patients receiving antibiotics. The

TABLE 8–2. Diagnostic Tests in Osteomyelitis

- Acute
  - Radiograph
  - Subperiosteal aspirate (preceded by skin culture)
  - Radionuclide[a] scan, if radiograph and aspirate are negative
  - Two blood cultures[b] (preceded by skin culture)
  - Bone culture in cases with radiographic changes
  - Hemoglobin, white blood cell and differential counts
  - Erythrocyte sedimentation rate
  - Chest X-ray
- Chronic
  - Sinus tract cultures
  - Bone culture

[a] Technetium first. If negative, gallium.

[b] One initially and one after subperiosteal or bone aspirate.

history and clinical features of the case should suggest the need for acid-fast, fungal, and other special stains and cultures. These factors should obviously be considered before the procedure. It is too late to think of an anaerobe after the specimen has been exposed to the air for several hours.

Radionuclide scans (Fig. 8–3) have revolutionalized the diagnosis of osteomyelitis because the uptake of technetium and/or gallium is enhanced from the earliest stages of localization of infection in bone.[95] False-positive results due to trauma and false-negative results due to ischemia have been reported, however, and complete reliance on this test can be hazardous. Furthermore, the examination does not provide any clue to the etiologic diagnosis.

At this time, measurement of antiteichoic acid antibodies (or other serologic test for staphylococcal antibody), and the demonstration of staphylococcal enzymes or cell wall antigens in the circulation, are not standardized and not sufficiently reliable for routine use.[85] Encouraging results using ELISA have been reported in the diagnosis of bone and joint tuberculosis.[91]

Treatment

Antimicrobial therapy of osteomyelitis depends on knowledge of the cause. Since *Staphylococcus spp.* are such predominant causes of acute hematogenous osteomyelitis in normal hosts, antistaphylococcal treat-

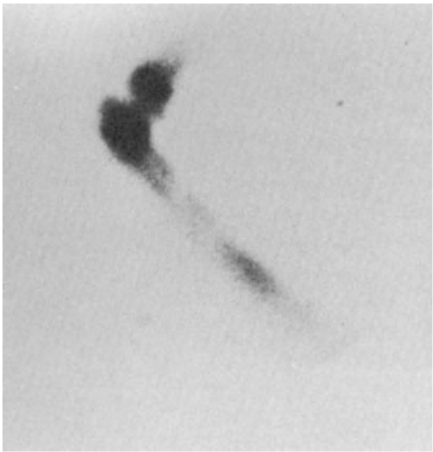

Figure 8–3. Osteomyelitis of mid-femur revealed by technetium scan. (Courtesy of Dr. A. Sullivan.)

ment is an accepted initial program for such patients. It is hoped that the majority of these will have some microbiologic evidence to support this assumption within a short period of time. Hence, the gram stain may show gram-positive cocci associated with neutrophils in pus aspirated from the subperiosteal site (or septic arthritis if there is a contiguous arthritis) or the blood culture may grow Staphylococcus within a day or two. Adjustments in drug choice, dose, route, and duration will then be facilitated. These decisions are also dependent on knowledge of absorption and drug penetration into bone.[95] The antistaphylococcal medications most useful include oxacillin, dicloxacillin, cloxacillin, and cephalexin. In certain circumstances it may be necessary to use clindamycin, and accept the additional risk of diarrhea and the theoretical disadvantage of a bacteriostatic drug. The rate of sterilization of the blood and local site (if accessible, as in biopsied cases) should be determined.

If failure of therapy is due to local abscess formation, then surgical treatment is indicated. This may be suggested by radiographic evidence of progressive osteolysis and sequestrum formation or the presence of extensive subperiosteal pus. In the patient who presents with acute hematogenous osteomyelitis and bone changes disease has been present for at least 10 days and he is a candidate for both surgical and medical management. Careful debridement, drainage of pus, and removal of foreign bodies (in certain cases) may be critical to the effectiveness of antimicrobial therapy.

There are some cases, however, that require consideration of additional antimicrobial therapy. Despite apparently adequate drainage and the fact that the doses of antistaphylococcal medication are sufficiently high, and reach expected therapeutic concentrations in the serum, some patients remain bacteriologically positive for prolonged periods. The reason in certain cases may be the presence of tolerant staphylococci.[57] These are bacteria that are insensitive to the normal killing effect of most of the aforementioned drugs. These staphylococci are not effectively killed, except by concentrations 8 or more times greater than those required to inhibit their growth. These tolerant bacteria may be susceptible to the effects of combined antistaphylococcal β-lactam drugs and aminoglycosides, such as tobramycin, gentamicin, or amikacin.[99] Another strategy is to use rifampin in combination with the primary antistaphylococcal drugs.[50] Others prefer to use fusidic acid in this situation. The risks of using both rifampin and fusidic acid are the development of resistant bacteria (particularly when these drugs are used alone) and the additional toxicities of these drugs. Fusidic acid, for example, is prone to cause thrombophlebitis when administered by peripheral vein for longer than 48 h.[41] Antagonism of the antibacterial effect is another potential pitfall of several of these combinations. The reader is referred to the specific recommendations on drug choice, dose, and side effects in Chapter 2.

Although drug choice is based on consideration of history and clinical features, and later on microbiologic findings, further antibiotic management of the case demands careful adjustment of dose, route, frequency of administration, and duration. Since therapy is expected to be at least 4 weeks, these special considerations seem justified in most cases. The dose and frequency are determined by measurements of the bioavailability of each drug and by adjustments to maintain a peak serum bactericidal titer of at least $1/8$ or peak serum antibiotic concentrations at least eight times the minimum bactericidal concentration (MBC). Although minimum criteria are not established, the frequency of administration should be adjusted to avoid prolonged periods of undetectable antibiotic activity in the serum. Evidence from experimental infection may be useful for the treatment of complicated cases.[59]

Osteomyelitis can be readily treated by the oral route, but this raises special considerations.[47] One is assurance of compliance. Others include determination of adequate drug absorption and followup of the patient. In most cases, these are achievable. We use verbal and written instructions as aids to compliance and also monitor this aspect of treatment by counting residual medication at each visit and through the use of a mail-in filter paper antibiotic assay strip. Adequate absorption is verified by use of the serum killing power or antibiotic assay of serum concentrations. The former test is easier to use if the patient's infecting organism is available. This test should be carried out at least weekly, once adequate absorption and a clinical response are established.

The duration of therapy for acute osteomyelitis currently recommended is a minimum of 4 weeks. This needs to be revised depending on the clinical and microbiologic (i.e., speed of bacteriologic eradication) outcome, and in consideration of cause, radiographic findings, and normalization of the erythrocyte sedimentation rate. Bone scans are not useful indicators of prognosis and cannot be used to guide the duration of therapy.[46] Patients diagnosed early, those infected with highly sensitive bacteria, and those with rapid sterilization of infected sites, few or no radiographic changes, steadily falling erythrocyte sedimentation rates, and rapid clinical improvement may require only 4 weeks of antibiotic treatment. Although the sedimentation rate returns to normal in a majority of patients within the first 4–6 weeks of infection, this is not always so and this should not constitute the only reason for prolongation of therapy.[15]

Chronic osteomyelitis usually requires antibiotic therapy for at least 2 months, with the same considerations as mentioned above. It is more likely that surgical intervention will be necessary in these cases. The duration of therapy may be shortened to 2 weeks in cases of Pseudomonas osteochondritis[42] or 4 weeks in cases of Pseudomonas osteomyelitis[86] after puncture wounds of the foot. Considering the long courses of treatment for both acute and chronic bone infection, some evaluation of the organs of metabolism and excretion of antibiotics should be made early and followed progressively. Hence, I recommend that renal and auditory function be monitored in patients receiving aminoglycosides for more than a week, and renal and hematologic function in patients receiving chloramphenicol and most other drugs. Those being treated with chloramphenicol, rifampin, and macrolides require liver function studies. Osteomyelitis associated with extensive tissue injury and ischemia after trauma may require additional surgical approaches including muscle flap and microvascular reconstruction.[51] Bone infections in these cases, and in patients requiring bone grafting or metal pins, usually require a minimum of 3 months of antibiotic therapy. If infection persists, progresses, or recurs after such a course, removal of foreign bodies and further debridement are usually needed.

Successful treatment of bone and joint tuberculosis usually requires three elements: surgical curettage, chemotherapy with at least two drugs (usually isoniazid and rifampin) for a minimum of 6 months, and immobilization for 6–12 weeks (vertebral infection may require longer periods of bed rest if instability is present).[64]

The treatment of fungal bone and joint infections is very difficult with existing agents. In a recent series only one of seven patients treated with ketoconazole for a minimum of 6 months was cured.[36] Surgical debridement is very important for these conditions.

The diagnosis and management of bone and joint infections is best achieved by a team approach. Radiographic, microbiologic, and surgical features of osteomyelitis emphasize the utility of this plan. Attention to nutrition, stabilization of underlying conditions, if any, and the psychosocial aspects of care for the child and family are critical in management and followup.

Immobilization of the affected bone is often helpful in relieving pain, although its role in healing is unclear. Bed rest may suffice in many infants and children, although splinting of the affected extremity is often necessary. In any case, frequent observation of the affected site is important in order to determine improvement in localized signs and recovery of function, and to ensure against development of local complications.

Although the question of whether disc space infection requires antibiotic therapy is controversial, we prefer to use antistaphylococcal drugs for the treatment of diskitis, since a number of studies have shown *S. aureus* to be present in some cases (see p. 583).

Prognosis

The prognosis for patients with osteomyelitis is considerably improved at present. The acute bacteremic stage is rarely associated with mortality or life-threatening complications. Localized complications, however, do occur. Involvement of the growth plate can be seen in infants with septic arthritis of the hip joint and contiguous osteomyelitis of the femoral epiphysis. Similarly, in patients under 1 year of age, some long bones have transepiphyseal blood vessels which allow spread of infection through the growth plate.[61] Uncontrolled, these complications can lead to limb shortening. Bones may be rendered unstable by osteolysis and progression of infection, with resultant pathologic fractures.

Chronic osteomyelitis is, of course, a complication of acute osteomyelitis. These patients may have recurrent activation of localized infection with pain, swelling and, occasionally, drainage at the initial site. Squamous cell carcinoma has been observed in approximately 1% of patients with osteomyelitis after an average delay of more than 30 years.[23] Despite these grave complications, children with acute osteomyelitis generally do well. Recently, more than 200 children were examined for long-term sequelae secondary to acute osteomyelitis.[2] Only nine had complications. Almost all of these could have been prevented by early diagnosis and treatment.

Arthritis

Inflammation of a joint is often a sign of serious local or systemic illness and requires careful consideration. Trauma is probably the most frequent cause of acute arthritis and is generally not a diagnostic problem because of historical features and the lack of systemic signs. However, both can be difficult to assess in the toddler; moreover, penetrating injury can precede septic arthritis.[5] Infectious arthritis is not a reportable disease (unless it is a component of gonococcal or tuberculous infection), so estimates of incidence are crude. Among hospitalized patients, we encounter joint infections about twice as frequently as bone infection, and the two occur together (or sequentially) in approximately 10% of cases.

Pathogenesis

Because little is known about the pathogenesis of arthritis in children it is difficult to explain the "targeting" of microorganisms to the joint space. Predisposing conditions include nonpenetrating or penetrating trauma (in the latter case the method of infection is by direct introduction of microorganisms and debris), chronic rheumatoid arthritis,[31] immunodeficiencies,[90] drug addiction,[28] and adjacent osteomyelitis. The latter is illustrated by the young infant with osteomyelitis of the proximal femur and spread of infection to the hip joint. This spread is facilitated by the fact that a relatively large part of the proximal femoral head and its blood supply are included within the joint space.

In the majority of cases of infectious arthritis the spread has occurred via the bloodstream. Thus the joint manifestation may represent the focus of infection or may be part of a more generalized process (Table 8–3). Erosion of articular cartilage results from several factors: increased pressure in the articular space, bacterial toxins (or other microbial cytotoxicity), lysosomal enzymes from synovial cells and neutrophils, and compromised vascular/metabolic supply.[76]

Immunopathic mechanisms are probably responsible for some of the postinfectious arthritis syndromes. These occur after a variety of common childhood infections. On rare occasions (more common in adolescents and adults) meningococcemia or gastroenteritis due to Shigella, Campylobacter,[32] Yersinia, or Salmonella[11] may be followed by migratory polyarthritis that can last or recur for as long as 6 months. The joint fluid in these cases is sterile and antibiotics do not affect the course of illness. Even more rarely, children develop conjunctivitis, urethritis, and polyarthritis, often called Reiter syndrome. The pathogenesis of both conditions is thought to represent immunologic injury in genetically pre-

TABLE 8–3. Pathogenesis of Septic Arthritis

- Direct spread
  - From adjacent bone
  - Penetrating wound
  - Furuncle/abscess
- Hematogenous
  - Monoarticular arthritis
  - Polyarticular arthritis
  - Part of systemic infection (pneumonia, meningitis, cellulitis, etc.)

disposed hosts (HLA B27 lymphocyte antigens are frequent in these children). Immune complexes also play a role in the pathogenesis of Lyme arthritis.[8]

Tuberculous bone and joint infection is still encountered in endemic areas, particularly among infants ingesting infected cow's milk.[63]

Etiology

The infectious causes of arthritis are listed in Table 8–4. Let me emphasize that, in North America, in normal hosts, *Staphylococcus aureus* infections account for most cases at all ages, and *Haemophilus influenzae* infections are equally as frequent in children under the age of 4 years. This is also true in Finland.[64] Nonetheless, the possible causes of septic arthritis are

TABLE 8–4. Etiology of Septic Arthritis

Cause	*Usual Age*
Bacteria	
Staphylococcus aureus	All ages
E. coli/Klebsiella	< 1 Month
Streptococcus, group B	< 2 Months
Haemophilus influenzae	6 Months–4 years
Streptococcus pneumoniae	> 2 Months
N. meningitidis	< 5 Years, > 15 years
N. gonorrhoeae	> 11 years
Other:	
Kingella kingae[26]	All ages
Propionibacterium acnes[103]	
Lyme arthritis[8]	> 2 Years
Fungi	
Candida[20,98]	< 1 Month, all ages with immune deficiency
Viruses	
Hepatitis B	> 1 Year
Rubella	> 10 Years
Arboviruses	All ages
Mumps	< 10 Years
Varicella[83]	< 5 Years
Herpes simplex/cytomegalovirus[24]	All ages
Coxsackie viruses[40]	
Epstein-Barr virus[71]	
Other	
Mycoplasma pneumoniae[82]	> 10 Years
Mycoplasma salivarium[88]	
Ureaplasma[92]	> 5 Years

so diverse that exact knowledge of the cause is critical to understanding the pathogenesis and significance of the joint infection, and to treatment and prognosis. Lactamase production by Staphylococci and Haemophilus underlines the need for accurate diagnosis, as do reports of unusual causes, such as Mycobacteria,[77] Moraxella,[21] Clostridia,[34,72] Micrococcus,[81] Listeria,[9] and Bacteroides,[1] and *Streptobacillus moniliformis* (rat-bite fever).[69] Polymicrobial septic arthritis is also noted on rare occasions.[65,72]

Rubella virus has been isolated from joint fluid both after natural infection and vaccination.[30]

As with osteomyelitis, specific etiologies can be suspected in certain hosts. Thus, group B *Streptococcus* are an important cause of arthritis in the first month of life, Salmonella in patients with sickle cell anemia, and *Neisseria gonorrhoeae* in sexually active women. Patients with underlying joint diseases are also prone to bacterial arthritis. Rarer examples include immunopathic arthritis in drug addicts with hepatitis B, opportunistic arthritis after intravenous injection of drugs in the same category of patients, and sporotrichosis in gardeners. Both septic and immunopathic (sterile) types of arthritis are noted during the acute and convalescent stages, respectively, of meningococcemia.[80]

Clinical Manifestations

Limp and fever are the hallmarks of bone and/or joint infections in patients of walking age with involvement of the lower extremities, hips, or sacroiliac joints. Restriction of movement of the affected extremity usually points to the source of the problem. This may be much less obvious in young infants in whom more subtle guarding of an extremity or asymmetric posture is present. Refusal to walk, irritability, and fever may be present in any of these situations and in patients with diskitis or sacroiliac arthritis.

Classic features of arthritis include localized swelling, redness, restriction of movement, and tenderness. Fluid in the knee joint may allow ballottement of the patella, a useful clinical sign. Careful measurement of the joint size will help in evaluating therapy and guiding decisions about drainage of joint fluid. The hip, knee, elbow, and ankle joints are most frequently involved. In some patients skin lesions are present or have been noted in their recent history. In others, trauma or upper respiratory infection precedes the onset of joint symptoms.

Lyme Arthritis

These children have recurrent attacks of asymmetric large joint swelling with fever, preceded by a papular erythematous rash over the extremities. The condition seems benign and symptoms rarely persist beyond 1 week in each episode. The condition, presumed due to a spirochete,[90] is transmitted in the summer and fall by ticks (*Ixodes dammini*) endemic to the northeastern United States.[8] Tetracycline treatment for 20 days (or longer, if symptoms persist) appears to shorten the course of illness and may prevent arthritis, myocarditis, and meningoencephalitis in some cases if therapy is begun at the stage of rash and fever.[89] Phenoxymethyl penicillin 50 mg/kg/day can be used in children under 8 years of age.

Diskitis

Back pain may indicate the presence of diskitis, although vertebral osteomyelitis, paraspinal abscesses and tumors, and renal disease need to be ruled out. Limp is common and may suggest hip infection in young infants. Occasionally, Gowers sign (child climbs to a stand by "walking" his hands up his shins, knees, and thighs), usually associated with muscular dystrophy, may be present.[45] The average age of these patients is 3 years, making localization of signs difficult.[22]

Radiographic findings include narrowing of the intervertebral space, but this may not occur for 3–8 weeks (Fig. 8–4). Radionuclide scans (particularly gallium-67) are most useful in localizing inflammation and making this diagnosis. Low-grade fever and mild systemic signs are often present and the erythrocyte sedimentation rate is usually elevated. Evi-

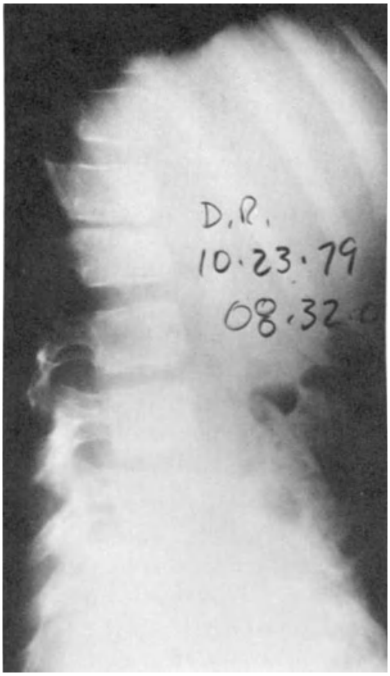

Figure 8–4. Disk space narrowing characteristic of diskitis. (Courtesy of Dr. A. Sullivan.)

dence of preceding or concurrent viral infection is often present; however, an infectious cause is rarely defined. When cultures of the disk have been obtained, *S. aureus* has been recovered most frequently, although Streptococcus, Moraxella,[102] and anaerobes have also been reported.[22]

Treatment of this condition is controversial, since rest, immobilization, and/or antibiotic therapy have all been associated with successful outcome. Tuberculosis should be ruled out in all cases. Once this is accomplished, we recommend dicloxacillin or another antistaphylococcal drug for approximately 4 weeks. Bed rest is usually sufficient, although some orthopedists prefer spica casts for selected patients. Progression of signs, osteolysis of vertebra, or failure to resolve within a week of bed rest or other immobilization, suggests the need for further investigation and consideration of alternative diagnoses. The majority of patients recover completely over a 2–4 month period. Long-term followup studies are needed to document the prognosis more accurately.

Sacroiliac Arthritis

It is estimated that sacroiliac arthritis accounts for approximately 1.5% of all cases of suppurative arthritis.[79] Most patients are boys 7–14 years of age, and *S. aureus* is the most common cause. Fever, low back and buttock pain, limp, and localized tenderness are common. Radicular sciatic pain is present in one-third of patients. Aggressive diagnostic procedures (aspiration and/or exploration of the affected joint) are important and evacuation of pus often necessary for recovery. Although osteolysis and synostosis are common, functional sequelae are rare. At least 4 weeks of antibiotic therapy is usually required.

Diagnosis of Arthritis

Even in the presence of extraarticular manifestations that clearly suggest the diagnosis (e.g., varicella, tuberculosis, coccidiomycosis), it is important to include examination and culture of the joint fluid (Fig. 8–5) as part of the initial diagnostic approach (Table 8–5). The purpose is to exclude the coexistence of two infections, to provide another excellent specimen to confirm the diagnosis of the systemic infection, and to better understand the pathogenesis (e.g., bacterial vs. immune complex) and therefore, the treatment and course.

The history and clinical examination may suggest systemic disease and the need for a lumbar puncture and/or viral cultures, urethral fluid examination and culture, etc. In newborns and young infants with arthritis it is often best to assume this manifestation is part of a systemic infection, and, therefore, to perform a lumbar puncture and obtain a urine culture, as well as to carry out the procedures described below.

The next step in the diagnosis of septic arthritis is to obtain a blood

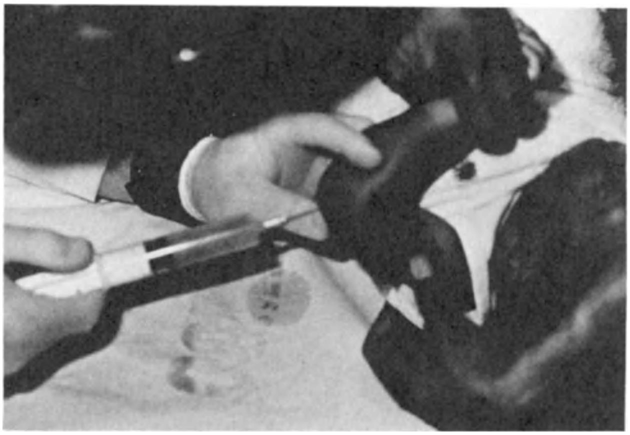

Figure 8–5. Needle aspiration of purulent joint fluid in patient with septic arthritis of the elbow. (Courtesy of Dr. A. Sullivan.)

culture and to culture samples of any suspicious skin lesion, genitourinary discharge, or other possible focus of infection. In the presence of skin lesions, eczema, or immune deficiency, it is also useful to take the precaution of culturing the prepared skin before obtaining the blood culture or joint fluid. The skin is prepared for both procedures in the classic way (i.e., application of alcohol to remove surface dirt, fatty acids, and some bacteria, followed by an iodophor antiseptic). Since these solutions do not sterilize the skin, culturing the needle entry site may aid the inter-

TABLE 8–5. Diagnostic Approach to Suspected Septic Arthritis

Blood culture[a]	One specimen before and one after arthrocentesis
Joint fluid examination[a]	Microscopic, using appropriate stains Presence of bacterial antigens Inflammatory markers Synovial fluid lactate[18] Culture appropriate for diagnostic possibilities
Serum, urine	Examination for bacterial antigen
Cerebrospinal fluid	Examination and culture when diagnosis suspected and in all newborns and young infants
Others	e.g., Skin, respiratory secretion, urethra, etc., depending on diagnostic possibilities in each case

[a] Obtain skin culture of prepared site before blood culture and arthrocentesis.

pretation of culture results such as "a few colonies of *Staphylococcus epidermidis*" in either the blood or joint fluid. If the organism was also present in the prepared skin after preparation, I would be more aggressive in searching for another cause for the arthritis.

Joint aspiration should be performed without use of local anesthetic, if possible, since this material can be bacteriostatic. If anesthetic is used, it is necessary to change the needle before entry into the joint space. Aspirated material is precious! It should be collected in sterile, clean tubes and transported to appropriate laboratories immediately. Refrigerator temperatures will often kill Neisseria; high temperatures (> 40°C) will likewise kill Haemophilus. Delays may also allow blood, local anesthetic, and inhibitors in pus (e.g., lactamase, lysozyme, complement) to render the culture useless. Preoperative clinical impressions are essential! Think about it, since only forethought will prompt most of us to include acid-fast, viral, fungal, or mycoplasmal cultures in selected cases. This must be selective in view of the complex and expensive array of tests available and the limited amount of diagnostic material in many cases. Even the request of "viral culture" of joint fluid without qualification is inadequate. This is because of the special procedures required for rubella, coxsackie A, and varicella, to name a few. Similarly, use of hypertonic media, antibiotic neutralizers, and special media (e.g., for Brucella, Pseudomonas, Yersinia) requires effective planning and communication with the laboratory. Joint fluid should also be examined quantitatively to document the degree and character of the inflammatory response (e.g., numbers and types of cells, glucose as a percentage of concurrent serum concentrations, and protein concentration). Preliminary studies indicate that synovial fluid lactate may help distinguish infective arthritis from noninfectious causes.[18] The cell type and numbers in synovial fluid may suggest certain diagnoses (e.g., viral arthritis with mononuclear cells, parasites with eosinophils) and can aid in following the evolution of the infection. It is often helpful to obtain a second blood culture after the arthrocentesis. Bacteria may be liberated into the bloodstream by the procedure and possibly cultured only from this source.

What can be done to make a rapid diagnosis of the cause of arthritis? The importance of microscopic examination of joint fluid cannot be overemphasized. Use of gram, acid-fast, and other stains is critical. Omitting this step in the diagnosis of joint infection is a grave error. The fluid, as well as serum and urine, should also be examined for Haemophilus, meningococcal, pneumococcal, and/or group B streptococcal antigen when these diagnoses are suspected.[52]

Radiographic examination of the affected joint and adjacent bones is useful to confirm the impression of fluid in the joint, although interpretation of these studies can be difficult. The examination may also reveal the presence of contiguous osteomyelitis or opaque foreign bodies or fracture, as may be seen in infectious arthritis secondary to trauma.

Radionuclide scans are useful to confirm the impression of inflammatory joint disease but cannot differentiate between the many causes of inflammation.[101] Occasionally, adjacent osteomyelitis or polyarticular involvement can be detected by such studies. These tests are usually not needed in uncomplicated cases of monoarticular septic arthritis. In the event of slow response of such cases to appropriate therapy, scans may be indicated to demonstrate radiographically negative osteomyelitis or other foci of infection. As I have done in the writing of this section, so should the physician expend his greatest effort in establishing an accurate etiologic diagnosis of arthritis. The treatment and prognosis depend on it! The practice of attaching a label of juvenile rheumatoid arthritis to children with enigmatic arthritis should be a last resort, since the implications are grave and long-standing and the diagnosis is often incorrect.

Differential Diagnosis

The patient may not have arthritis at all. For example, bursitis may cause swelling and inflammation over a joint that is difficult to differentiate from joint infection. Superficial fluctuance and painless joint movement are useful signs, but needle aspiration of the joint space may be required in some cases. Staphylococci and Streptococci are the most frequent pathogens in these lesions.[62] Drainage and antibiotic therapy for 5 days after sterilization of the local infection site is highly effective.[37]

The diagnosis of arthritis in the presence of negative or inadequately examined cultures is indeed problematic. Consider the long list of conditions that may affect joints (Table 8–6). History, the age of the patient, and physical diagnosis should exclude the majority of the possibilities, but not all. Recurrent, migratory polyarthritis may also be seen in patients with sickle-cell anemia.[33] What are the causes of bacteriologically negative arthritis in which neutrophils predominate in the synovial fluid? Before calling this "aseptic arthritis"[55] or monoarticular juvenile rheumatoid arthritis,[6] consider several other explanations as well (Table 8–7). Consideration and investigation of these possibilities will often avoid unnecessary therapy, procedures, and followups. As in other situations, there are risks, but also rewards, in limiting the use of antibiotics in children with bacteriologically negative "septic arthritis."

Treatment

Initial therapy of septic arthritis in infants and young children (under 4 years) should include administration of antibiotics active against both Staphylococcus and Haemophilus. My preference for intravenous therapy includes oxacillin 200 mg/kg/day plus chloramphenicol 75 mg/kg/day, both divided q 6 h. If the patient is allergic to penicillin, cephalothin 100 mg/kg/day divided q 6 h and chloramphenicol can be used. Moxalactam,

TABLE 8–6. Differential Diagnosis of Noninfectious Arthritis

- Hypersensitivity
  - Drug
  - Serum sickness
  - Anaphylactoid purpura
- Metabolic
  - Gout
  - Hyperparathyroidism
  - Ochronosis
  - Acromegaly
  - Agammaglobulinemia
  - Hemochromatosis
- Degenerative
  - Osteoarthritis
- Neurogenic
  - Syringomyelia
  - Diabetes mellitus
  - Nerve injury
  - Leprosy
- Bleeding
  - Hemophilia
  - Trauma
- Neoplasms
  - Synovioma
  - Pigmented villonodular synovitis
  - Giant cell tumor of tendon sheath
  - Leukemia
- Bone
  - Aseptic necrosis
  - Neoplasm
  - Osteochondritis
  - Hypertrophic osteoarthropathy
- Miscellaneous
  - Pseudogout
  - Familial Mediterranean fever
  - Tietze syndrome
  - Behçet syndrome
  - Bursitis
- Cause
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
  - Scleroderma
  - Dermato-polymyositis
  - Sarcoidosis
  - Psoriasis
  - Ulcerative colitis
  - Regional enteritis
  - Whipple disease

TABLE 8–7. Explanations for the Appearance of Neutrophils in Synovial Fluid in the Presence of Negative Bacterial Cultures

Prior antibiotic use
Local anesthetic
Immunologic arthritis (postinfectious, hepatitis, inflammatory bowel disease, collagen-vascular disease)
Rheumatoid arthritis
Rheumatic fever
Tuberculosis
Adjacent infection
Viral arthritis
Mycoplasma
Fastidious bacteria
Sickle-cell anemia[33]

cefotaxime, or cefoperazone can be substituted for chloramphenicol. Dicloxacillin 100 mg/kg/day, divided q 6 h, and chloramphenicol are recommended if the patient is able to take medication orally. Oral therapy is preferred because of patient acceptability, decreased morbidity, reduced costs, excellent bioavailability (especially chloramphenicol), and adequate synovial fluid concentrations.[58] Even aminoglycosides penetrate well into synovial fluid (e.g., 50% of serum concentrations for gentamicin and tobramycin); hence, intraarticular administration of antibiotic is rarely indicated.[14]

Other drugs should be selected for initial therapy if specific diagnoses are suggested. For example, the presence of numerous gram-positive cocci in the joint fluid usually indicates that Staphylococcus is causative, although anaerobic bacteria should be kept in mind. In the first 2 months of life this gram smear may also represent group B streptococcal infection. Arthritis in persons of that age group should be considered part of a systemic infection and initial therapy should include oxacillin and gentamicin (see Chapter 2 for details) until the extent of infection has been determined. In these cases, rapid diagnosis of group B streptococcal infection can be made by demonstration of antigen in joint fluid, urine, serum, or CSF. If it is found, penicillin should be used in place of oxacillin. Unless the strain is tolerant, the aminoglycoside (gentamicin) is discontinued after sterilization of the infected sites has been documented (usually 3–4 days).

The dose and type of antibiotic should be adjusted as soon as possible, in keeping with microbiologic results demonstrating etiology and susceptibility. Efficacy should be monitored by the assurance of a peak serum killing titer of at least 1/8. Reduction of the dosage may be appropriate when the bacterial pathogen is highly susceptible and high serum killing titers (e.g., 1/128 or more) are achieved. A note of caution: a serum killing power of at least 1/8 is only a guideline. Thus attempts to maintain an exact titer should be resisted. If this level is not achieved, the dose of drug can be increased, the route or drug may require change, or probenecid can be added for antibiotics secreted by the proximal renal tubules (penicillins, cephalosporins). Absorption and compliance should be monitored in patients receiving oral therapy.

A minimum duration of 2 weeks of antibiotic therapy is generally recommended for bacterial arthritis. Tuberculous and fungal arthritis, and those complicated by contiguous osteomyelitis or other extraarticular infections, require longer individualized regimens, as do immunocompromised patients. Of course there is nothing magic about a duration of 2 weeks and slightly shorter courses are appropriate in situations where rapid clinical, bacteriologic, and inflammatory resolutions are noted. The latter is monitored by serial examination of the inflammatory characteristics of the joint fluid, if available, and by Wintrobe erythrocyte sedimentation rates. A fall in the sedimentation rate is a reassuring clue to successful resolution, although this is sometimes inconsistent and subject to many influences.

Drainage of joint fluid is recommended in certain situations. As much fluid as possible should be removed at the initial diagnostic aspiration (with gentle, nontraumatizing technique!). Involvement of the hip joint in young infants, painful reaccumulation of fluid in other joints, contiguous osteomyelitis, immunocompromised hosts, and unusual pathogens often constitute indications for surgical drainage of purulent material.

Immobilization and analgesia are useful in the early stages of infection. The former is sometimes accomplished by bed rest, but splinting, casts, and skin traction have been used as well. Percutaneous pin traction and casts that prevent easy examination of the joint should not be used.

Decisions about the duration of hospitalization depend on the degree of incapacitation of the patient, the need for surgical management, and the route of antibiotic therapy. I treat patients at home as much as possible. Compliance is encouraged by verbal and written instructions and monitored by telephone calls, office visits, and a mail-in urine filter paper antibiotic assay.

Followup and Prognosis

Followup of 49 children treated for septic arthritis between 1965 and 1975 identified 13 with sequelae.[39] Eight had severe impairment of ambulation. This is a particular risk for patients with hip infection. In my more recent experience, and that reported from Finland,[65] residual handicaps are less common after early diagnosis and appropriate therapy of infectious arthritis. Nevertheless, careful followup for at least a year is important if relapse, chronic infection, or osteomyelitis of the adjacent bones are to be detected early. Radiographs of the joint and surrounding bones should be performed approximately 6–8 weeks after therapy. Clinical or radiographic signs may indicate a need for further studies.

Residual defects seen after acute arthritis include capital femoral necrosis, articular surface degeneration, ankylosis, and limb shortening. The very long-term outlook after septic arthritis in children is unknown. To date there are no reports to suggest a predisposition of these patients to the development of recurrent infection or degenerative arthritis.

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9

Neurologic Infections

Meningitis

Although a relatively uncommon infectious disease, meningitis is one of the most severe. In the United States approximately 30,000 infants and children develop bacterial meningitis yearly, and as many as 10% of these die. One-third have permanent long-term complications.[145] Add to these three times as many children with viral meningitis, as well as those suffering from tuberculous, fungal, and other causes of meningeal inflammation, and the toll becomes even greater. Genetic factors play a role, as witnessed by reports of intrafamilial disease[43] and the high incidence of Haemophilus meningitis in Alaskan Eskimos.[235]

In most cases there is an overlap between encephalitis and meningitis, since inflammation of the meninges is rarely confined to that anatomic site. This is particularly true for many of the viral infections, such as those caused by mumps or enteroviruses. In such cases, both meninges and brain tissue are involved in the pathologic process. Neonatal meningitis is discussed in Chapter 3.

Although carriage of meningococcus is infrequent in infants and children, rarely exceeding 3%,[155] high rates of acquisition and illness may occur during outbreaks of meningococcal infection.[76]

Pathogenesis

Although in the preantibiotic era meningitis was frequently associated with direct spread of infection from adjacent foci, at present the infection develops predominantly after bacteremia. Finding bacteria in the blood and cerebrospinal fluid (CSF) of an ill child, however, does not ensure that the pathogenic sequence is as described above. Hence, a careful search for contiguous foci as a source of direct spread of bacteria to the subarachnoid space is important in every case. This should include examination of the middle ear, mastoids, facial and nasal areas, base of the neck and spine, and sinuses. It is particularly difficult to examine the nasal septum for bony or mucosal defects.[59] Neurenteric fistulae and dermal sinuses may also be difficult to define.[151] Patients with traumatic head injury may not have obvious CSF leaks through the nose or ear, yet may have clinically apparent or inapparent skull fractures that set the stage for subsequent meningitis. Meningitis has also been seen in patients with brain tumors and in patients with chronic gastroenteritis and marasmus.[248] In the vast majority of cases, however, the pathogenesis of meningitis is unknown, but appears to represent a focal manifestation of systemic infection and bacteremia. Perhaps the absence of complement, and, therefore, reduced CSF opsonic activity, predisposes the host to meningitis should bacteria lodge in the blood vessels of the meninges.[253] Impaired host defenses may also account for the occurrence of meningitis in some immunocompromised and debilitated hosts.[12]

Most of the pathology of bacterial meningitis is localized to the meninges, although adjacent cerebral swelling and vascular inflammation are commonly present as well. The latter may be reflected by focal cortical necrosis, cerebral infarction, and atrophy.[221] Some of these changes can be demonstrated by computerized tomography (CT) at a fairly early stage.[21] This test may also reveal some of the other pathologic brain changes present in meningitis, such as cerebral swelling and an increase in the size of the ventricles and cisterns. Although meningeal inflammation is often the most prominent sign, much of the neuronal injury occurs secondary to vasculitis, thrombosis, cerebral hypoxia, and cerebritis.

Etiology

The infectious etiologies of meningitis are outlined in Table 9–1. The causes of meningitis in the newborn are distinctive and are discussed in Chapter 3. Patients with trauma to the central nervous system (CNS), immunocompromised hosts, and those with indwelling shunts and/or other foreign bodies, as well as those with abnormal anatomy (e.g., meningomyelocele) may also be infected with staphylococci and gram-negative bacteria including Acinetobacter.[17] Listeria meningitis may be seen in patients beyond the newborn period. Those with haemochromatosis are at high risk,[231] as are those with other chronic underlying conditions.[23] Polymicrobial anaerobic meningitis may be seen with meningoenteric fistulae.[233]

The three major bacterial pathogens of meningitis in infancy and childhood are *Haemophilus influenzae, Streptococcus pneumoniae,* and *Neisseria meningitidis.*[89] All serogroups of meningococcus have been involved,[97] as have other species of Neisseria.[238] Enteroviruses (ECHO and coxsackie in in-

TABLE 9-1. Infectious Etiologies of Meningitis

Viruses		
	Enteroviruses (ECHO, coxsackie, polio)	
	Mumps	
	Adenovirus	
	Arboviruses (Eastern Equine, St. Louis, California, encephalitis virus)	
	Lymphocytic choriomeningitis virus	
	Measles	
Bacteria		
	S. pneumoniae	
	H. influenzae	
	N. meningitidis	
	Group B Streptococcus	Newborns
	E. coli	
	Other Enterobacteriaceae	
	Listeria monocytogenes	
	Leptospira	
	Anaerobic bacteria	
	Staphylococcus aureus	
	Mycobacterium tuberculosis	
	Streptococcus pyogenes (group A)[165]	
	Haemophilus parainfluenzae[83]	
	Haemophilus aphrophilus[152]	
	Aerococcus viridans[173]	
	Pasteurella ureae[130]	
Fungi		
	Histoplasma	
	Candida	
	Cryptococcus	
	Coccidioides	

dustrialized countries, and poliomyelitis in areas with inadequate immunization) are still the most common causes of meningitis, although frequently less severe in manifestations and outcome.

Mumps was formerly the cause of many cases of meningoencephalitis year-round. Now that the disease can be prevented by vaccination, enteroviruses account for many more cases. Adenoviruses, arboviruses, and, occasionally, lymphocytic choriomeningitis virus may also be causative.

One of the most devastating forms of meningitis is due to tuberculosis, a fact often forgotten in North America.[163] Worldwide, tuberculous meningitis is still a major cause of death (mortality rates remain around 40%) and morbidity.[48] Unfortunately, the disease is extremely difficult to diagnose and progresses rapidly in children.[174] Most cases are due to *Mycobacterium tuberculosis*; however, sporadic cases due to *M. bovis* are occasionally reported in raw milk drinkers.[120]

Anaerobic bacterial meningitis is rare.[102] When present, both staphylococcal meningitis[196] and anaerobic bacterial meningitis are often associated with chronic otitis media or sinusitis, neurosurgical procedures or the presence of foreign bodies (including CSF shunts), abdominal trauma, or immunosuppression. In hosts presenting with these features anaerobic cultures should be included in the diagnostic evaluation. Meningitis has also been reported as a complication of Fusobacterium septicemia.[1] Dual infections are extremely rare, but both bacterial and viral,[112] as well as mixed bacterial meningitis (e.g., *Haemophilus influenzae* and *Clostridium perfringens*) has been reported.[88]

Clinical Manifestations

Mortality, and much of the morbidity, of bacterial meningitis are seen in situations where the diagnosis is made late. The reason is that clinical manifestations of meningitis, in infancy in particular, are nonspecific. Thus, poor feeding, anorexia and vomiting, irritability, and irregular respirations are common. Seizures, bulging fontanel, and neck stiffness are late signs. Older patients report headache, confusion, change in mentation, lethargy, and neck pain. Photophobia or other visual abnormalities may also be noted in patients old enough to report it. Depending on the location of the initial site of infection, other neurologic signs may also be present. These include cranial nerve palsies, ataxia, and alterations of consciousness.

Differentiating the patient with meningitis from the vast majority of young infants with fever and some of the above nonspecific signs is often difficult. The frequency of meningitis is extremely low, yet the consequences are grave. Hence, it is reasonable to examine the CSF whenever one is in doubt about the cause of fever in an infant under 2 years with irritability and some of the above signs, as well as in the patient whose first seizure is associated with fever. Many of the causes of fever (e.g., pneumonia, otitis media, cellulitis, arthritis) may be associated with meningitis as well. There are different ways to look at this. Looking at patients with meningitis, Samson found that 11/27 presented with clinical features compatible with febrile seizures.[204] All of these patients were under 16 months of age. On the other hand, only 14/304 patients with febrile convulsions had meningitis or developed it shortly thereafter.[149] Again we are left with the dilemma of justifying many lumbar punctures in order to diagnose bacterial meningitis. Considering the extreme morbidity associated with bacterial meningitis, and the low risks of lumbar puncture, including the theoretical possibility that the procedure may induce meningitis in bacteremic patients,[225] the spinal tap seems preferable. Rare side effects of lumbar puncture include epidural abscess, vertebral osteomyelitis, bleeding, and retroperitoneal abscess.[142]

Since many of the features noted above are nonspecific, can the physical findings help us? It is relatively easy to suspect meningitis when the patient has a stiff neck (Brudzinski sign) or pain on straight leg raising (Kernig sign), but less easy when there is a suggestion of a high-pitched cry, fever, slight hyperreflexia, and irritability. In the presence of a bulging fontanel, seizures, cranial nerve palsies, or petechiae (suggesting bacteremia due to *Neisseria meningitidis* or, less commonly, *Haemophilus influenzae*), the diagnosis of meningitis is more likely.

Diagnosis

Cerebrospinal fluid is defined as normal if there are fewer than 30 cells/mm^3 (90% mononuclear) in the first month of life and fewer than 5 cells/mm^3 thereafter. The CSF glucose concentration should be 50% or greater than the concomitant peripheral blood glucose and the protein concentration may be up to 200 mg/dl in the first week of life and less than 40 mg/dl after the first month. Lumbar puncture should be performed after the peripheral blood sugar level is determined, as the stress of the lumbar puncture may elevate the serum concentration of glucose to an abnormal level. A time period of 30–90 min is usually required for equilibration of glucose concentrations in the CSF and peripheral blood glucose compartments.

Laboratory confirmation of the presence of meningitis is dependent on the lumbar puncture. Table 9–2 outlines some of the diagnoses that need to be considered in patients with CSF pleocytosis. Examination of CSF in 98 patients after noninfectious causes of generalized convulsions

TABLE 9–2. Causes of CSF Pleocytosis

- Meningitis
  - Bacterial (including tuberculous)
  - Viral
  - Fungal
  - Amebic
- Cerebritis
- Chemical (e.g., methotrexate)
- Cat scratch disease
- Mastoiditis
- Sinusitis
- Epidural abscess
- Vertebral osteomyelitis
- Epidermoid cysts
- Abnormal communication of the subarachnoid space with skin (e.g., dermoid sinus), gastrointestinal tract (e.g., neurenteric fistula), etc.
- Convulsion-induced (rare)
- Cerebral infarction[216]

revealed pleocytosis in only 2 (12 and 65 WBC, respectively), with normal concentrations of glucose and protein.[64] Lumbar puncture should be considered in infants and children with the above clinical presentations and whenever the blood culture is positive for *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Salmonella, Escherichia coli,* group B Streptococcus, Listeria, and even *Candida albicans.* These organisms are selected because of their propensity to invade the CNS. The likelihood of meningitis is increased in certain hosts, including newborns and younger infants, and in patients who are immunosuppressed, have hemoglobinopathies, or are malnourished.

If the patient has a foreign body in place, such as a ventriculoperitoneal shunt, then *Staphylococcus epidermidis* and other opportunistic pathogens need to be added to the list. These patients often present with vomiting and malfunctioning of their shunt, although low-grade fever, loss of appetite and weight, and other nonspecific signs may be present for days to weeks before the CNS signs are manifest.

CSF should be examined by gram stain (Fig. 9–1) (acid-fast stain if tuberculosis is suspected). A newly developed ELISA may prove useful for the detection of mycobacterial antigen in CSF and other body fluids.[201] At times bacteria may be seen in normal CSF.[81,164] Simultaneous blood and CSF glucose levels should be measured. A diffusion gradient of CSF/serum of less than 40% is highly suggestive of bacterial infection.[54] The CSF protein concentration is less useful diagnostically, but is important in following the course of the patient's illness (Table 9–3).

In patients with suspected meningitis a blood culture as well as a culture of any appropriate skin or other infected focus that may have caused, or be associated with, the meningitis should be performed. Included in this

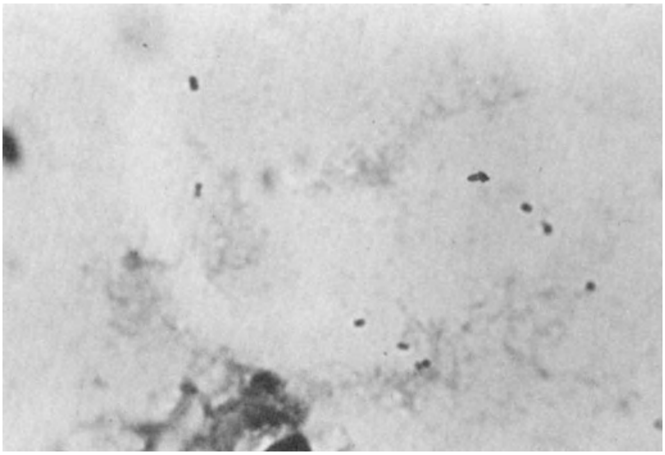

Figure 9–1. Gram-stained appearance of *N. meningitidis* in the CSF.

TABLE 9-3. Causes of Elevated CSF Protein Concentration

- Infectious
  - Bacterial (including tuberculosis) meningitis
  - Viral meningitis or encephalitis
  - Fungal meningitis
  - Brain abscess
  - Cerebritis
  - Syphilis
  - Mumps meningoencephalitis
- Noninfectious
  - Hypernatremic dehydration
  - Subdural effusion
  - Cerebral hemorrhage
  - Thrombosis
  - Tumor

category are tympanocentesis or myringotomy in cases of otitis media associated with bacterial meningitis. Diagnostic aspiration and drainage of sinuses and mastoids, periorbital abscesses, etc., should also be carried out early, in the presence of meningitis. This is because of the danger of continuous seeding of the meninges and brain tissue from these sites.[42] Antibiotics will not effectively prevent or cure infection under such circumstances, and deaths have been reported in situations where drainage was not included in the management of these patients.

The CSF should be examined for the presence of Haemophilus, pneumococcal, and meningococcal antigen by a rapid immunologic technique. Latex agglutination,[45] staphylococcal coagglutination,[55] and counterimmunoelectrophoresis are all useful; however these assays are relatively insensitive in detecting group B Meningococcus and several types of pneumococci. Bacterial antigens can also be found in the urine and sera of many of these patients. These studies are critical in patients who have had previous antibiotic therapy but, considering their convenience and low cost, should be included in the diagnostic evaluation of all cases of meningitis.

The CSF should be centrifuged at 1500 × *g* for 15 min and the sediment cultured.[170] Cultures should include penicillinase if the patient has been previously treated with penicillin, or other penicillinase susceptible antibiotic. Hypertonic medium is also useful for culturing wall-defective bacteria induced by penicillins, cephalosporins or other cell-wall-active antibiotics. Anaerobic cultures are indicated in newborns[29] and in debilitated and immunosuppressed patients, and in those with dermal sinuses,[91] and traumatic/surgical lesions of the CNS. Historical and clinical features may suggest the need for other diagnostic laboratory procedures and microbiologic tests.

Diagnosis of Viral Meningitis. The presence of polymorphonuclear leukocytes in the CSF is highly suggestive of bacterial meningitis, as is a low glucose concentration. However, it should be remembered that both of these features are present in tuberculous meningitis and can be present in viral, fungal, and amebic infection as well. During outbreaks of enteroviral infections, it may be worthwhile to repeat the lumbar puncture after a 6–12-h period of observation without antibiotic therapy in order to differentiate viral from bacterial meningitis. In one study 87% of such patients were noted to have a shift from polymorphonuclear to mononuclear cells in their CSF, thus facilitating the diagnosis of viral meningitis.[77] This is extremely important in reducing morbidity and in determining the prognosis and need for followup studies. It is very rewarding to manage a 3- or 4-year-old child in this fashion, and to be able to send the patient home with confidence and without treatment on the following day. Contrast this with the usual prolonged hospitalization, treatment, and followup ordinarily required for children with bacterial meningitis.

In such cases cultures to detect the presence of viruses should be performed on CSF samples. Throat and rectal swabs may also show the presence of enteroviruses, which can often be cultured within a few days.

Other tests to differentiate bacterial from viral meningitis, such as CSF lactate,[200] are useful but cannot be relied upon completely. Endotoxin assays can be used to detect gram-negative bacteria in the CSF. Of course, pneumococcus, group B Streptococcus and Staphylococcus will not be detected this way. Although as many as two-thirds of children with *H. influenzae* have anemia (hemoglobin less than 11 g/dl) at the time of diagnosis, this is also a nonspecific finding.[176]

Treatment

Treatment of bacterial meningitis depends on knowledge of the etiology. Table 9–4 lists the common causes and appropriate treatments for meningitis at various age groups. There is some debate about the initial therapy of meningitis in the age group of 1–3 months, in particular. In one large review, group B Streptococcus and Listeria were commonly found;[252] however, Haemophilus may also be causative,[71]

Ampicillin and chloramphenicol may be antagonistic against group B Streptococcus.[237] In a smaller series,[153] group B Streptococcus were not reported in infants older than one month. We prefer to use ampicillin and amikacin, or ampicillin and cefotaxime, in such situations, since *Haemophilus influenzae*, pneumococcus, and streptococcus may also be causative.[10]

Once the etiology is defined, the drugs outlined in Table 9–4 can be used as appropriate for each infectious agent. In the United States, penicillin should be used to treat pneumococcal meningitis, whereas chloramphenicol is preferred in countries where strains of pneumococci have

TABLE 9–4. Antibiotic Treatment of Bacterial Meningitis

Age		*Etiologies*	*Treatment*
0–30 Days	Common	Group B Streptococcus	Ampicillin + amikacin
		E. coli	Ampicillin + amikacin *or* Ampicillin + cefotaxime
		Listeria	Ampicillin + amikacin
		Unknown	Ampicillin + amikacin *or* Ampicillin + cefotaxime
30–60 Days	Common	Group B Streptococcus	See above
		Listeria	See above
		S. pneumoniae	Ampicillin, penicillin, cefuroxime, cefotaxime, *or* ceftriaxone
		H. influenzae	Ampicillin + chloramphenicol *or* moxalactam *or* ceftriaxone[49] *or* cefuroxime *or* cefotaxime
		N. meningitidis	Penicillin
		Salmonella	Ampicillin + amikacin *or* moxalactam + amikacin
		Unknown	Ampicillin + moxalactam *or* cefotaxime
2 Months–5 Years		*H. influenzae*	See above
		S. pneumoniae	See above
		N. meningitidis	See above
		Unknown	Ampicillin + chloramphenicol *or* ampicillin + moxalactam *or* ceftriaxone
> 5 Years	Common	*N. meningitidis*	See above
		S. pneumoniae	See above
		H. influenzae	See above
		Unknown	Ampicillin *or* ceftriaxone *or* cefuroxime *or* cefotaxime

evolved that are either highly or relatively penicillin-resistant or resistant to multiple antibiotics.[177] Ampicillin is effective against some pneumococci relatively resistant to penicillin. When chloramphenicol is used, the oral route is preferred (once the patient's condition is stable enough to permit oral administration of food and drugs) since the drug is most bioavailable by this route. This should be done in hospital, and the serum and CSF (when available) concentration of drug should be measured to ensure that adequate (at least 4–8 times the MIC) but nontoxic (less than 25 μg/ml in the serum) concentrations have been achieved. All other antibiotics usually employed in the treatment of meningitis (except for antituberculosis drugs) must be given intravenously. The duration of therapy is arbitrary; however, most experience is with courses of at least 7 days.[169] Some prefer to use as a guideline 1 week after defervescence. Persistence of pleocytosis in the CSF is common and should not be used as an indication for prolonged antibiotic therapy.[40]

On the basis of adult experience, intraventricular aminoglycosides may be used in older children (over 1 year of age) with gram-negative bacillary (not Haemophilus or meningococcus) meningitis.[121] In rare instances, such as meningitis due to methicillin-resistant Staphylococcus or Klebsiella, intravenous trimethoprim/sulfamethoxazole may be useful.[104]

Persistence of bacteria in the CSF is rare after 24 h of therapy except in cases of neonatal meningitis (Chapter 3) and in patients with shunt infections or gram-negative enteric meningitis. If bacteria are still present, host factors need to be considered and quantitative susceptibilities should be repeated. One should look for unusual bacteria, such as *Streptococcus pneumoniae* relatively resistant to penicillin,[3] ampicillin-resistant β-lactamase-negative Haemophilus,[178] or chloramphenicol-resistant Haemophilus. Two cases of persistent meningitis associated with dexamethasone treatment have also been reported.[27]

Tuberculosis. The CSF in patients with tuberculous meningitis usually contains mostly lymphocytes, however, neutrophils may predominate early in the course. Its sugar concentration is decreased, whereas the protein concentration is often markedly elevated.[183]

Patients with tuberculous meningitis should initially receive at least three drugs: isoniazid, rifampin, and ethambutol.[128] In patients who may be infected with resistant strains of *M. tuberculosis* pyrazinamide should also be included in the initial regimen. These drug therapies can then be adjusted on the basis of in vitro susceptibility tests. Adrenal corticosteroids may be prescribed at this stage of tuberculous meningitis, since symptomatic relief may be more quickly achieved. However, this is a controversial issue.[62] It is not clear whether this therapy improves the overall prognosis of this devastating infection.

Poor prognostic factors include stage 3 coma at the time of admission, age under 3 years, associated miliary tuberculosis, and delay in initiation of therapy.[48] The presence of tuberculomas may also delay response to therapy.[139]

Nonantibiotic Therapy. Beginning a discussion of the treatment of meningitis with antibiotic therapy is somewhat in error. In fact, most of the mortality and acute morbidity in meningitis is referable to causes other than direct bacterial effects. Diagnosis and management of perturbations of blood pressure, fluid and electrolyte balance, and CNS status are essential. Continuous observation of the patient in the first few days is mandatory because the prevention and early treatment of shock, disseminated intravascular coagulation, cerebral edema, seizures, aspiration, and hypoxemia are critical. Irreversibility is quickly seen when the diagnosis of these conditions is delayed. Hence, blood pressure, pulse, and mental status of these patients should be monitored as frequently as every 15 min (or continuously, if possible) for the first 8–24 h of therapy.

A low cerebral perfusion pressure is an ominous sign, indicating that cerebral edema and increased intracranial pressure are severe enough to reduce blood flow with resultant cerebral ischemia.[94] Acute cerebral edema is best managed by the administration of oxygen and mannitol 1.5 g/kg intravenously over 20 min. Cardiorespiratory management is essential should tentorial, uncal, or cerebellar herniation occur. In such cases, intubation, hyperventilation, and intravenous mannitol should be given. Neurosurgical approaches (ventriculostomy, craniotomy) may also be required in patients with herniation and persistent or progressive abnormalities of blood pressure, breathing, and pulse despite the aforementioned treatments.

One other consideration often forgotten is the fact that many patients presenting with meningitis may not have eaten and may have vomited frequently. Thus these patients are quite dehydrated. The tendency to limit fluids because of the fear of inappropriate secretion of antidiuretic hormone (ADH) can seriously compound this dehydration.[192] I have seen patients develop CNS injury secondary to thrombosis, most likely due to restriction of fluids and severe dehydration in the early stage of meningitis. In fact, it is less common to have inappropriate ADH secretion in the first 24 h of meningitis than after 48–72 h of illness. If one has to choose, some fluid retention is preferable to extreme dehydration in such cases. Thus, patients who are in shock, those who are dehydrated, and those who have continuing fluid losses (e.g., marasmic patients with gastroenteritis) should be treated with relatively large amounts of fluid. Arterial and venous catheterizations to determine adequate intravascular pressures and volumes is required in such cases. Urinary output should also be measured quantitatively by means of a urinary catheter. Walking the thin line between intravascular hypovolemia and fluid retention and cerebral edema is a delicate therapeutic challenge.

If the above described severe complications are not present, and the patient is stabilized within the first 12–24 h, mild fluid restriction generally will obviate the problems created by inappropriate ADH secretion. This can be suggested by a reduced serum concentration of sodium. Edema may be noted in periorbital and dependent areas. Gallop rhythm, pulmonary edema, hepatomegaly, and seizures are late signs of fluid retention.

Seizures are also prevalent among patients with meningitis. Their management is controversial because the double-edged sword here consists of the noxious effects of seizures on the one hand and the risks of anticonvulsant therapy on the other. Depressing the sensorium in a patient with meningitis may complicate further diagnosis and management of the case. Therefore, I recommend diazepam 0.1–0.2 mg/kg intravenously to stop the acute seizures, along with oxygen and careful attention to the patient's cardiorespiratory status. The smallest dose (given by intravenous infusion) of diazepam that stops the seizure should be used. If the seizures are recurrent or prolonged, or if there is a previous history of seizures, phenytoin or phenobarbital can be added for continuing anticonvulsant prophylaxis. Phenytoin causes less neurologic suppression, but takes a longer period of time to achieve effective serum concentrations than does phenobarbital. Doses of 10 mg/kg can be used initially at a rate of 1 mg/kg/min intravenously. The addition of phenobarbital increases the risk of respiratory arrest in patients already receiving diazepam.

If seizures and other neurologic signs are due to cerebral edema, then a trial of mannitol and dexamethasone is useful. Mannitol (1.5 g/kg over 20 min intravenously, in patients with adequate urine output) will be followed by a diuresis and, often, some amelioration of the CNS signs. Urea (0.5 g/kg q 12 h intravenously) can also be used.[47] If this is effective, the dose may be repeated three or four times during the acute stage. This is an appropriate time to begin dexamethasone (0.5 mg/kg/day divided q 6 h IV × 3 days) as well. The dexamethasone begins to produce an effect 8–12 h after it is initiated. This may also assist in reducing cerebral edema in such patients.

Measurement of head circumference and transillumination of the skull are important components of the initial physical examination, and should be repeated periodically throughout the management of infants with bacterial meningitis. Similarly, hearing, vision, and other neurologic functions should be assessed as soon as it is feasible. Persistent fever (i.e., beyond 5 days after initiation of therapy) is a common problem encountered during therapy for meningitis (Table 9–5). Nosocomial infections,

TABLE 9–5. Causes of Persistent Fever in Patients with Bacterial Meningitis

- Phlebitis
- Nosocomial infections
- Extrameningeal infection
    - Otitis media
    - Arthritis
    - Osteomyelitis
    - Pneumonia
    - Pericarditis
- Subdural effusion
- Dehydration
- Hydrocephalus
- Drug fever

phlebitis, and sterile subdural effusions are most frequently responsible. The presence of fluid in the subdural space during the first few days of meningitis may be due to subdural empyema, hence the need for early diagnostic aspiration and drainage in this circumstance. The indications for aspiration of the subdural space later in the course of recovery are clinical signs (e.g., fever *plus* vomiting, seizures, focal neurologic signs, or systemic toxicity) or persistent or progressive CSF inflammatory changes. The majority of subdural effusions associated with meningitis are self-limited.

Complications

Pneumococcal meningitis is probably the most virulent of the three common causes of bacterial meningitis of children. Approximately one-third of these patients present with convulsions. Neurologic sequelae, including deafness, hydrocephalus, seizures, and retardation occur in one-half of survivors.[135] Death (in approximately 10% of cases) is seen mostly in infants under 1 year who also have pneumonia and extreme hypoglycorrhachia.

Many of the acute complications outlined above are summarized in Table 9–6. Focal neuropathies may include spinal cord lesions.[92] Blindness is often of a cortical nature and may be reversible, but deafness is often permanent. Rarely pyogenic endophthalmitis may be present due to *H. influenzae.*[224] Patients with persistent focal neurologic deficits often have brain infarction demonstrated by CT.[57] The prognosis in such cases is poor.

Some of the late complications of meningitis are outlined in Table 9–7. Hearing,[198] vision,[51] and motor defects are most damaging. Ataxia slowly but steadily improves but is often associated with hearing loss.[122] Hearing loss is seen in as many as 10% of patients with bacterial men-

TABLE 9–6. Acute Complications of Bacterial Meningitis

Shock
Disseminated intravascular coagulation
Cerebral edema
Seizures
Dehydration
Inappropriate secretion of antidiuretic hormone
Extrameningeal infection (e.g., pneumonia, pericarditis)
Gastritis (can be hemorrhagic)
Duodenal ulcer
Hypoglycemia
Subdural empyema
Cerebral infarction[218]
Internal carotid artery occlusion[160]

TABLE 9-7. Late Complications of Bacterial Meningitis

Hydrocephalus
Seizures
Weakness/paralysis
Deafness
Ataxia
Learning disorders
Psychomotor retardation
Cortical blindness
Optic atrophy
Diabetes insipidus[87]
Anterior pituitary dysfunction[87]
Subdural effusion
Brain abscess (rare)[78]

ingitis and visual impairment in about 3%.[180,211] It is usually necessary to follow patients for at least 1 year after meningitis to define fully the extent of neurologic injury, if any. Auditory brain stem responses are an effective means of testing hearing in infants. Differentiation of complications due to neurologic damage from those due to the psychologic trauma of hospitalization and life-threatening illness may be impossible. Families and patients require careful and continuous counseling after their child has had meningitis and other hospitalizations.[133] The prognosis is improving, however, and charts, such as those shown in Fig. 9–2 for meningococcal meningitis, should be used to illustrate the fact that more than 50% of survivors of all types of bacterial meningitis are normal.[67] The figure may be as high as 99% for enterovirus infections. Focusing attention on the positive outcome and liberal use of physiotherapy, occupational therapy, remedial hearing aids, and psychologic therapy for learning disabilities, behavior problems, and the like may also reduce the frequency of major morbidities formerly described with meningitis.

Recurrent Meningitis. Repeated episodes of meningitis are noted in fewer than 1% of all cases,[207] and relapses may occur with any etiology and treatment, including use of new antibiotics.[25] Skull fractures, with or

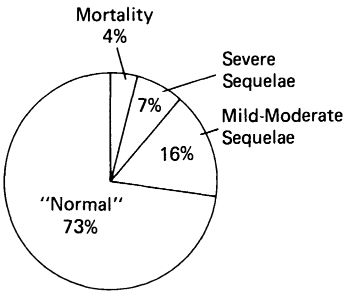

Figure 9–2. Outcome in children with meningococcal meningitis.

without CSF leakage, are important causes. Many small dural tears heal spontaneously, but isotope studies and surgical explorations are indicated in posttraumatic cases with meningitis, the latter particularly for recurrent infection.[137] Prophylactic penicillin four times daily is recommended if dural tears are possible. Although these episodes occasionally represent the child's unfortunate experience with two separate, but unrelated, infections (e.g., Haemophilus meningitis followed by enterovirus meningitis), other reasons should be sought (Table 9–8). For example, repeated episodes of meningococcal meningitis are suggestive of complement[46] or IgG_2-subclass deficiencies.[9] CT scans may reveal epidermoid cysts[34] or meningocele[103] in patients with repeated episodes of sterile meningitis. Radioisotope scans can be used to detect cribriform plate and other communicating defects in some of these children.[86]

The diagnosis of Mollaret meningitis denotes an idiopathic condition and should be made only after thorough exclusion of other possible causes. These cases should be periodically reviewed and new developments in diagnosis applied. In this way many cases have been reclassified as immune or anatomic defects, or due to infections, such as herpes simplex.[219]

Chronic Meningitis. Chronic meningitis has many causes, most of them rare.[66] These include parameningeal focal abscesses,[119] enteroviral meningitis in immune-deficient patients,[105] and autoimmune conditions resembling juvenile rheumatoid arthritis.[72]

Prevention

Since the risk of spread of *H. influenzae* to household contacts under 6 years of age is approximately 500 times greater than for children in the general population,[234] a program of chemoprophylaxis is recommended

TABLE 9–8. Causes of Recurrent Meningitis

Posttraumatic
Dermal sinus
Cribriform plate defect
Neurenteric fistula
Other fistulae
Epidermoid cyst
Mollaret meningitis
Cryptococcus
Coccidioidomycosis
Tuberculosis
Complement deficiency
IgG_2-subclass deficiency
Penicillin-resistant pneumococcal meningitis

as an adjunct to patient education and observation[213] (Table 9–9). Day-care centers can be very large; hence limitation of prophylaxis to the classroom contacts (all ages, including staff) is most practical. Special efforts to attain a high degree of compliance are important to ensure success of these programs.[167] I prefer to administer the rifampin to the index case beginning at the time the other antibiotic is discontinued, in order to avoid confusion about the interpretation of rashes, nausea, fever, and other toxicities. Others add rifampin during the last 4 days of meningitis therapy. Two prices may be paid for prophylactic antibiotic regimens. One is the development of *H. influenzae* resistant to rifampin[175] and the other is a false sense of security that such prophylaxis is 100% effective; it is not.[22] Approximately 25% of carriers remain positive 1–4 weeks after rifampin prophylaxis.[166]

Chemoprophylaxis should also be instituted in all household and day-care contacts of patients with meningococcal infection.[185] Since contacts of all ages are susceptible, rifampin is given for 2 days to all close contacts. Others who have been in direct contact with the patient's respiratory secretions or CSF should also receive the drug. All contacts should be told of the signs and symptoms of meningococcal disease and warned to seek early medical attention should these be noted, even up to a month after the contact has occurred. Although nosocomial transmission is rare,[8] isolation procedures including washing hands and mask are used during the first 24 h of treatment in cases of *Haemophilus* and meningococcal meningitis. Thereafter, these patients (and all patients with pneumococcal meningitis) are not likely to be a source of nosocomial spread of infection.

Aseptic Meningitis

Definition/Epidemiology

Aseptic meningitis can be defined as the presence of fever, neck stiffness and pain, CSF pleocytosis, and negative routine bacterial cultures. On the basis of this definition, in the summer and fall months the vast majority of infants and children with meningitis have infection with enteroviruses.

TABLE 9–9. Prophylaxis for Contacts of Invasive *H. influenzae*

Indications
  1. *H. influenzae* type B invasive disease in index case *plus*
  2. Household or day-care center contacts ≤ 4 years of age

Method
  1. Rifampin 10 mg/kg/dose b.i.d. × 4 days to all contacts (including non-pregnant adults)
  2. Follow meningitis therapy of index case with above rifampin regimen
  3. Clinical surveillance

In most instances, when using the term aseptic meningitis, we are referring to viral meningitis. Nevertheless, the differential diagnosis according to the above criteria encompasses a wide range of conditions (Table 9–10).

Viral meningitis is seen worldwide and involves individuals of all ages; however, recent surveys suggest that infection in very young infants is being recognized more frequently. For example, in a recent survey in San Antonio 79% of the patients with viral meningitis were under 1 year of age.[223] Several viruses, such as echovirus 6, echovirus 11, and adenovirus may be prevalent in the community simultaneously.[239] The prognosis of viral meningitis is generally benign; however, recognition of the disease in newborns and young infants, and its differentiation from bacterial meningitis and other causes of seizures and fever, are very important.

TABLE 9–10. Etiology of Aseptic Meningitis

- Viruses
  - Enteroviruses
  - Mumps
  - Epstein-Barr virus
  - Herpes simplex
  - Lymphocytic choriomeningitis virus
  - Arboviruses
  - Adenoviruses[126]
- Bacteria
- Mycoplasma[74]
- Fungi
- Protozoa
- Chlamydia[95]
- Rickettsia
  - Rocky Mountain spotted fever (*R. rickettsii*)
- Miscellaneous
  - CNS leukemia
  - Craniopharyngioma and other cysts[181]
  - Postneurosurgery[33]
  - Chemical
    - Methotrexate
    - Azathioprine[147]
  - Sulfonamide[132]
  - Parameningeal infection
  - Cat scratch disease
  - Behçet syndrome
  - Lupus erythematosus
  - Multiple sclerosis
  - Mucocutaneous lymph node syndrome

Etiology

The etiologic spectrum of aseptic meningitis is wide (the reader is also referred to the etiologies of meningitis listed in Table 9–1). Notwithstanding the diverse list of causes, in North America most cases are due to enteroviruses (usually ECHO or coxsackie),[245] while mumps is responsible for many cases year-round in developing countries.

Clinical Manifestations

The clinical manifestations of aseptic meningitis are similar to those of bacterial meningitis, although usually milder in nature. Fever, headache, and vomiting are the major signs. Nuchal rigidity is variable, as is neck pain. Some outbreaks of enteroviral infection are associated with nonspecific or characteristic skin rashes, whereas others cause more encephalopathy and even polio-like syndromes.[39] Examples of the former are erythematous macular or petechial rashes seen with various types of echoviruses; the latter include the vesicles seen in the hand, foot, and mouth syndrome due to coxsackie viruses.[245] Specific clues to the etiology of aseptic meningitis may also be garnered from other signs and symptoms, such as adenoviral conjunctivitis,[126] or those noted in infectious mononucleosis, mucocutaneous lymph node syndrome, or Rocky Mountain spotted fever.

Diagnosis

The classic features of the CSF in patients with aseptic meningitis include mild pleocytosis (usually fewer than 1000 white blood cells/mm^3), a predominance of lymphocytes, a normal glucose concentration, and normal or elevated protein concentrations. Unfortunately, this is not true for all cases. Hence, the status of the CSF may range from completely normal[239] to one in which there are more than 2000 white blood cells/mm^3, of which more than 60% are polymorphonuclear.[215] Younger patients often have more CSF pleocytosis.[25] In one report, the CSF in 18% of 103 patients contained more than 2000 white blood cells/mm^3 in the CSF, 21% had greater than 60% polymorphonuclear leukocytes, and 12% had a protein concentration of greater than 80 mg/dl.[215] A CSF glucose concentration $<$ 50% of the peripheral blood glucose has also been reported for most of the viral causes of aseptic meningitis including herpes simplex, ECHO, and coxsackie viruses.[223] Occasionally, the presence of white blood cells in the CSF may reflect a viral cytopathic effect, as illustrated by the presence of radially segmented monocytes.[144]

As one can see, the CSF findings in patients with viral meningitis may be extremely variable. Hence it is important to obtain appropriate viral cultures. Viruses are found in up to 60% of CSF specimens appropriately cultured, and in over 80% of patients with enteroviral meningitis when results of viral cultures of the throat and stool are also included.[239] The importance of confirming a viral cause for these cases is reflected by many benefits including a decrease in hospitalization and in use of antibiotics.[38]

Many methods have been used in an attempt to differentiate viral from bacterial causes of meningitis. A second lumbar puncture within 6–12 h of the initial one is very useful.[77] If the initial CSF contains a majority of polymorphonuclear leukocytes, repeated examination of the CSF will often show a shift to a predominance of mononuclear cells without a dramatic increase in the total number of cells. This is a fairly consistent finding in meningitis due to viral causes. Less direct means of ruling out a bacterial diagnosis, such as the measurements of serum C-reactive protein[184] and CSF lactic acid concentrations,[190] have yielded inconsistent results. For example, lactic acid elevations can also be seen in the CSF of patients with diabetic coma, increased intracranial pressure due to trauma and other causes, and cerebrovascular accidents.[28] Falsely low concentrations can also be seen with bacterial meningitis.

Meningoencephalitis due to mycoplasma is rare but can be severe and prolonged. The diagnosis is most often made serologically; however, cross-reactions with brain antigen may complicate interpretation of this test.[129] If possible, respiratory and CSF mycoplasma cultures should be obtained.

Management

Treatable causes of aseptic meningitis, such as tuberculosis, leptospirosis, Rocky Mountain spotted fever, and herpes simplex virus infection should be ruled out initially (a careful history will suffice in most cases). Occasionally, mycoplasma and neoplasia will fall into this category as well. The vast majority of cases of aseptic meningitis, however, are due to viruses and require no specific therapy. Careful management and accurate diagnosis will avoid prolonged hospitalization, unnecessary use of antibiotics, and needless diagnostic procedures. The rest of the treatment of such patients depends on the extent of neurologic impairment and is similar to procedures used for the treatment of bacterial meningitis and viral encephalitis.

Isolation need not be very strict, and careful handwashing should be adequate in most cases. The contagiousness of enteroviral meningitis is low, with familial spread present in fewer than 10% of instances.

Prognosis

The prognosis of aseptic meningitis reflects the underlying cause and, more important, the extent of neurologic impairment. In addition, immunocompromised patients may develop fatal meningoencephalitis due to common enteroviruses.[41] In most cases, the long-term outcome is benign. However, delays in speech and language development are occasionally noted after meningitis in newborns and young infants, and behavior and learning problems in older children, particularly when seizures are associated with the acute illness.[75] Some newborns demonstrating jitteriness and seizures secondary to coxsackie B5 infection have also been found to develop spasticity and decreased intelligence.[73] Conversely, enterovirus infections in the first 3 months of life were associated with a normal IQ score in another survey; however, some decrease in receptive language functioning was apparent.[246] Awareness of the potential for behavior problems (due to the infection and also probably due to hospitalization, parental attitudes, etc.) should also be kept in mind.

Fungal Meningitis

Epidemiology/Etiology (Table 9–11)

Meningitis due to fungi is rare in normal infants and children. On the other hand, opportunistic infections with *Candida albicans* and other fungi are becoming more common in severely debilitated newborns, immunocompromised patients, and in others with trauma or intracranial surgery. One of our patients, for example, developed Candida meningitis 3 weeks after surgery for a craniopharyngioma.[37] Exposure to pigeons and bird roosts suggests the possibility of cryptococcus infection[108] or histoplasmosis. Outbreaks of the latter have also occurred in communities during times of demolition and construction.[241] Patients in developing countries and those living in warm climates have increased opportunities for invasion by a wide variety of chromomycoses. Similarly, in immunosuppressed patients fungal meningitis may be associated with aspergillosis (usually *A. fumigatus*) and mucormycosis (usually Rhizopus or Mucor). The latter is particularly often associated with poorly controlled

TABLE 9–11. Fungal Causes of Meningitis

Candida sp.
Histoplasma capsulatum[189]
Cryptococcus neoformans
Coccidioides immitis[24]
Paracoccidioidomycosis (South American Blastomycosis)[168]
Blastomycosis (*B. dermatididis*)[138]
Aspergillosis (*A. fumigatus*)[11]
Mucormycosis (*Rhizopus, Mucor sp.*)
Chromomycosis (Phaeohyphomycosis), e.g., Cladosporium *sp.*, Hormodendrum *sp.*, Phialophora *sp.*, Drechslera *sp.*,[250]

diabetes mellitus in adults; however, cases can occur in juvenile diabetic patients as well.[118] Many body sites may be infected by Mucor type fungi (Rhizopus, Absidia, Mortierella, and Mucor). Pulmonary and rhinocerebral involvement are most common, and the latter most life-threatening.[140] All in all, fungal meningitis is, fortunately, a rare condition, usually associated with encephalitis, and requires a high index of suspicion for diagnosis.

Clinical Manifestations/Diagnosis

The onset of fungal meningitis is usually much more insidious than that of bacterial or viral meningitis or meningoencephalitis. The pathologic lesions are generally granulomatous, and involve any portion of the brain, including meninges, brain stem, or cerebellum. CT scans are useful in defining the site of infection; however, diffuse granulomatous meningeal involvement may not be easy to define in its early stages. A lymphocytic CSF pleocytosis is often present; however, polymorphonuclear leukocytes do not rule out the diagnosis. Patients with cryptococcal meningitis will have decreased glucose and elevated protein concentrations in the CSF. Both *Coccidioides immitis*, and *Histoplasma capsulatum* may invade the meninges as part of disseminated disease; however, meningitis may also be the only manifestation. Increases in complement-fixing antibodies in the serum and, especially, in the CSF, are very helpful in the diagnosis of these two infections.[189] Demonstration of cryptococcal antigen in the CSF is more specific. Culture of the CSF or appropriate parameningeal tissues should be obtained in all cases.

Management

Treatment of fungal meningitis requires the use of intravenous amphotericin B (see Chapter 2). 5-fluorocytosine should be added to the program whenever possible. Often, the use of combinations of amphotericin and 5-fluorocytosine allows the administration of lower doses of each drug, which provides the advantages of synergistic activity in many cases, and reduction in toxicity of each drug.[37] Combination therapy (amphotericin and 5-fluorocytosine) is recommended for candidal and cryptococcal meningitis in particular.[14]

Coccidioidal meningitis requires intrathecal therapy for at least 1 year. An Ommaya reservoir is inserted and amphotericin B is instilled directly. Occasionally, miconazole can be used in a similar fashion when treating fungi sensitive to this drug.[96] Systemic antifungal therapy is usually added, although the need for it is not clear in all cases. Use of high-dose oral ketoconazole may simplify this approach for some patients.[44] In fact, some children have been successfully managed with large oral doses of ketoconazole (15–22 mg/kg/day) plus intraventricular miconazole (3–5 mg in 1–2 ml 5% dextrose-water) instilled through a ventriculoperitoneal shunt.[101] Caution is urged to avoid antagonistic combinations of antifungal drugs.

Consultations with infectious disease and neurology departments are recommended in these unusual infections. In many cases, such as mucormycosis and chromomycosis, surgical excision of focal lesions is an important component of the treatment program. Antifungal therapy is usually maintained for at least 3 months in the treatment of fungal CNS infection, and often longer than a year with coccidioidomycosis and cryptococcosis. Improvement correlates with a fall in the titer of CSF antigen in cryptococcosis, and CSF antibody in coccidioidomycosis. Careful followup is necessary for all of these conditions, since relapses are not uncommon, even after prolonged therapy (e.g., cryptococcal meningitis after 7 months of ketoconazole).[187] Intrathecal therapy via an Ommaya reservoir may be required for the management of relapsing cryptococcal meningitis. A careful search for underlying immune defects and predisposing illnesses should be carried out in each case of fungal infection of the central nervous system.

Eosinophilic Meningitis

The presence of eosinophils in cerebrospinal fluid usually indicates an allergic or infectious etiology (Table 9–12). Hypersensitivity to the pres-

TABLE 9–12. Eosinophilic Meningitis

- Parasites
  - Dirofilaria
  - *Taenia solium*
  - *Paragonimus westermani*
- Bacteria
  - Chronic meningitis
  - Pneumococcus
  - Syphilis (*Treponema pallidum*)
- Fungi
  - *Coccidioides immitis*
  - Candida
- Viruses
  - Lymphocytic choriomeningitis virus
  - Coxsackievirus
- Other
  - Foreign body (especially rubber)
  - Hodgkin disease[106]
  - Lymphoma
  - Myeloproliferative disorders[114]
  - Chemical

ence of a variety of parasites, foreign bodies, chemicals, and viruses[35] may also be associated with the presence of eosinophils and IgE in the CSF. Among the infectious agents that should be searched for are lymphocytic choriomeningitis virus, suggested by the exposure of the child to mice, gerbils, or hamsters.[36] Chemical causes such as iophendylate dye used for myelography may also be associated with eosinophilic meningitis.[156]

Central Nervous System Shunt Infections

Etiology/Pathogenesis

Infections of CNS shunts occur in approximately 25% of patients, usually within 2 months of surgical insertion.[209] In fact, two-thirds of cases occur within a month of operation.[90] Most of these are due to *Staphylococcus epidermidis* or *Staphylococcus aureus*;[209] however, a variety of other organisms, including gram-negative bacteria,[212] and other skin flora can be causative (Table 9–13). Ventriculoperitoneal or ventriculoatrial shunts, used to relieve hydrocephalus, are most frequently infected; however, indwelling reservoirs for the treatment of malignant and chronic fungal infections may also become contaminated.[229]

Clinical Manifestations

Presenting signs include low-grade fever, vomiting, irritability or lethargy, and other signs of increased intracranial pressure. The onset is often insidious, but can be more acute, particularly if shunt malfunction is also present. Neck stiffness is uncommon. Patients may also develop recurrences or second infections within a few months of an initial episode.

TABLE 9–13. Etiology of CNS Shunt Infections

- *Staphylococcus epidermidis*
- *Staphylococcus aureus*
- Gram-negative bacteria[212]
  - *E. coli*
  - *P. aeruginosa*
  - *Klebsiella pneumoniae*
  - *Morganella sp.*
  - *H. influenzae*[141]
- Diphtheroids[179]
- *Propionibacterium acnes*[13]
- *Streptococcus pneumoniae*[214]

The symptoms and signs of shunt infection are referable to the age of the patient, the infecting microorganism, the degree of surgical trauma, and other underlying conditions of the host. Ventriculoperitoneal shunt infections may present with signs of acute peritonitis, predominantly due to infection of the intraperitoneal end of the shunt.[110] Symptoms associated with bacteremia can range from general malaise to shock.

Diagnosis

Shunt infection should be suspected in any child with an indwelling CNS drainage system and fever. A percutaneous aspiration of CSF from the shunt reservoir should be performed, unless an obvious reason for the fever is readily found. In such cases, lack of a prompt response to treatment of the underlying infection should also prompt shunt aspiration. If infected, the CSF usually has fewer than 1000 white blood cells/mm^3, a moderately elevated protein level, and reduced glucose concentrations. However, again, these vary with the duration of the infection, the age of the patient, and the nature of the infecting microorganism. Bacteremia is often present, although it is unclear whether this is the primary event or occurs secondary to the shunt infection.

Although not in common usage, serologic markers of shunt infection can be found by following serum agglutination titers to *Staphylococcus epidermidis* and C-reactive protein concentrations.[107]

Patients with shunt infection may also have hypocomplementemic proliferative glomerulonephritis due to immune-complex deposition in their kidneys.[179] This is generally mild and reversible, although some patients may have permanent renal damage, particularly if their shunt infection has been long-lasting.

Treatment

Treatment of shunt infection needs to be tailored to meet the specific susceptibilities of the infecting microorganism and the need to obtain high concentrations of antibiotics within the CSF and shunt system. This is most commonly achieved by a combination of systemic and intraventricular antibiotics (Table 9–14). Since Staphylococcus is such a common cause of infection, systemic nafcillin[232] is often used initially, although vancomycin can also be very effective. Rifampin may be used to supplement either the penicillins or vancomycin, if a tolerant Staphylococcus is isolated, and/or if response to therapy is slow.[195] Intraventricular antibiotics should be added for the treatment of staphylococcal and most gram-negative enteric bacterial infections. These can be instilled daily into the shunt reservoir or through a ventriculostomy, if the shunt is removed because of malfunction. Successful treatment of shunts without removal has been achieved[232] and this experience justifies a trial of com-

TABLE 9–14. Intraventricular Antibiotics Useful in the Treatment of CNS Shunt Infections

Drug	*Daily Intraventricular Dose (mg)*	*Comment*
Cephalothin[214]	50–100	Larger dose with functioning shunt. Accumulation of drug may occur; monitor CSF concentrations.
Gentamicin[188]	1–2	Other aminoglycosides may also be used.
Nafcillin[232]	75	
Methicillin[232]	100	

bined systemic and intraventricular antibiotics for a 3–4-day period. If clinical improvement and sterilization of the site are not seen, then removal of the shunt is usually required. This depends somewhat on the underlying organism, as gram-negative bacteria are the most difficult to eradicate. An exception is *Haemophilus influenzae,* which may be treated with systemic chloramphenicol and without removal of the shunt in some cases.[193] This is particularly true for nontypable strains.[141]

Tailoring antibiotic regimens on an individual basis is best. This depends on quantitative MIC and MBC data on the infecting organism. The objectives should be to achieve microbicidal concentrations of drug within the CSF and to eradicate the organisms without loss of function of the shunt. When intraventricular therapy is used, daily administration is necessary until sterilization of the CSF is noted. CSF inhibitory and bactericidal titers (fungicidal if appropriate) or CSF drug concentrations should be measured. Cultures should be allowed to incubate (in nutritious growth-supporting media, e.g., hypertonic media for bacteria treated with cell- wall-active antibiotics) for a minimum of 72 h. Thus, intraventricular therapy will be prolonged for 3 days beyond sterilization in most cases. Parenteral therapy should then be continued for an additional week in patients who respond quickly, and for 2 weeks in patients who have a slower response and in those infected with gram-negative bacteria other than *Haemophilus influenzae.*

Prognosis

The mortality associated with shunt infections has markedly decreased to approximately 6%.[90] Mortality may be as high as 39%, however, with highly pathogenic gram-negative bacteria.[212] Although the CSF may be sterilized, it is not unusual to see the persistence of white blood cells and hypoglycorrhachia for several weeks. This is probably a reflection of slowly resolving inflammation related to both the foreign body and the infectious process, and should not be an indication for continuing antibiotic therapy.

The long-term outlook for patients with CNS shunt infections is complicated. Patients with these infections may be the ones who have undergone more complicated surgery and have more complicated underlying hydrocephalus and neurologic disease. With these qualifications in mind, it is apparent that those patients with recurrent infection have a more serious reduction in intelligence and psychomotor functioning, as compared to patients with shunts that are not infected.[159] Shunt infections may also be associated with CSF loculations and malfunctioning of the drainage systems.

Prevention

Administration of antibiotics perioperatively is indicated in most cases. In institutions where staphylococci are the common causes of shunt infections, methicillin or cephalothin is useful.[158] These antibiotics should be begun intravenously within the hour before surgery and continued for approximately 48 h. There is some evidence that nafcillin may be preferable to these drugs, since better CSF penetration may be achieved.[157] In populations where gram-negative bacteria are common causes of these infections, intraventricular instillation of an aminoglycoside pre- and postoperatively may also be useful. Meticulous surgical technique and careful sterilization of shunt hardware are, of course, important components in the prevention of infection in these patients.

Encephalitis

Encephalitis refers to inflammatory conditions of the brain in which alterations of consciousness, headache, fever, vomiting, and focal neurologic signs predominate. This is distinct from meningitis, in which neck and back stiffness and pain, fever, and vomiting are most frequently encountered. However, there is often involvement of both brain and meninges (meningoencephalitis).

The pathogenesis and etiology of encephalitis are extremely variable. When infectious agents are involved, geography, epidemics, and several host factors affect the cause. This is a dynamic situation and requires constant surveillance for proper identification of the infectious causes in any community. For example, a recent survey in Finland indicated that the majority of identifiable causes of encephalitis in that country were due to herpes simplex virus (32% of cases in 1978).[131] Yet, in the summer season, in most countries, enteroviruses cause many more cases of meningoencephalitis. Several of the causes of encephalitis are listed in Table 9–15. Many of these are discussed in relation to the systemic infection, such as measles, subacute sclerosing panencephalitis, rubella, and varicella (Chapter 7). Some, such as toxoplasmosis, rarely occur in normal subjects,[109] but are being reported more frequently in association with pneumocystosis, cytomegalovirus infection, and mycobacterial infection in patients (mostly adults) with AIDS and related syndromes.[150]

TABLE 9–15. Infectious Causes of Encephalitis

- Viruses
  - Herpes simplex
  - Epstein-Barr virus
  - Enteroviruses
    - Coxsackie
    - Echo
    - Polio
  - Mumps
  - Arboviruses
  - Adenoviruses
  - Measles
  - Influenza
  - Varicella zoster
  - Rabies
  - Respiratory syncytial virus
- Amebae
  - *Naegleria fowleri*
  - *Acanthamoeba castellani*
- Fungi
  - Cryptococcus
  - Histoplasma
- Protozoa
  - Toxoplasma
  - Trypanosomes
  - Malaria
- Chlamydia
  - Psittacosis
- *Mycoplasma pneumoniae*
- Bacteria
  - *M. tuberculosis*
  - Leptospira
- Rickettsia
  - Rocky Mountain spotted fever
- Postinfectious
- Postimmunization
  - Pertussis
  - Measles

Epidemiology

The vast majority of cases of encephalitis are due to viruses. Sometimes these infections are epidemic in nature, as is the case with arboviruses. Reservoirs for this group of viruses are often birds; accidental transmission to horses and man by various insect vectors is possible. Hence, equine encephalitis viruses are commonly present in quail, pheasants, and partridges, and transmitted to horses and man by mosquitoes. Groundhogs are the reservoirs for a rare cause of arbovirus encephalitis, Powassan virus, which is reported in Ontario and New York.[68]

Host factors determine the expression and progression of viral infection of the brain as well. This has been discussed in regard to progressive encephalitis secondary to measles virus, and can also be seen due to ECHO and adenoviruses in patients with hypogammaglobulinemia.[161]

Etiology (Table 9–15)

Herpes simplex virus is the most common sporadic cause of encephalitis in humans, and is discussed separately. Enteroviruses more commonly cause aseptic meningitis or meningoencephalitis, and rarely manifest as isolated encephalitis. Now that poliomyelitis is preventable by effective vaccination, coxsackie and ECHO viruses probably account for most cases of meningoencephalitis in developed countries.

Arboviruses may cause large outbreaks of encephalitis and other illnesses. For example, St. Louis encephalitis caused 36 deaths among 229 cases in Mississippi in 1975.[191] Of these patients 58% had encephalitis, 15% aseptic meningitis, 21% undifferentiated febrile illnesses, and 6% a variety of focal neurologic manifestations. In marked contrast, there were only 16 cases of arbovirus infections reported in the entire United States in 1982.[199] Some are known by various names, such as tickborne, Far Eastern, Russian, spring-summer, and Central European encephalidities, even though the arbovirus and tick vector are the same. Other arboviruses sometimes encountered in the United States include Eastern and Western Equine, St. Louis, LaCrosse, and California Encephalitis. Included in the latter group are the Jamestown Canyon virus and several other subtypes. Powassan[247] and Venezuelan Equine Encephalitis viruses can also be seen.

In addition to the above mentioned causes of encephalitis, it is worthwhile to keep Epstein-Barr virus in mind, considering the possibility that antiviral therapy against herpes viruses might be effective in treatment of this condition as well. These patients may have infectious mononucleosis, suggesting the diagnosis, or encephalitis may occur without any other manifestations of mononucleosis, yet be due to Epstein-Barr virus infection.[99] Facial and brachial palsy, peripheral neuritis, transverse myelitis, cerebellitis, hemiplegia, optic neuritis, and Reye and Guillain-Barré syndromes have also been noted with infectious mononucleosis.[7] Rarely, combined infection (e.g., measles and Epstein-Barr virus) may cause encephalitis.[162] Respiratory viruses, including influenza and respiratory syncytial virus, may occasionally be associated with encephalitis.[32]

Encephalitis can also occur after immunization, such as pertussis encephalopathy within a few hours to a few days of the vaccination. More common is encephalitis after varicella, or after natural infection or immunization with rubella, measles, or mumps. Herpes zoster-associated encephalitis is rare and seen almost exclusively in immunosuppressed elderly patients.[117] Such cases usually occur within 1 month of the immunization or acute illness, with the patient remaining healthy between vaccination and the occurrence of the signs of encephalitis. These patients have less fever, headache, and vomiting than patients with acute infectious encephalitis.[127] Although smallpox vaccination was formerly associated with postvaccinal encephalitis, this condition should be only of historical interest, considering the abandonment of smallpox vaccination worldwide. Some cases of apparent postinfectious disease may, in fact, represent latent, progressive, or reactivation infection.[53] Cat-scratch disease, recently considered of bacterial origin, may also be a cause of acute encephalopathy.[228] This diagnosis should be made only after exclusion of treatable causes.

Clinical Manifestations

Encephalitis is usually associated with headache, vomiting, fever, irritability, lethargy, and alterations in consciousness. Disorientation, focal neurologic signs, and seizures may also be present, as may nystagmus, ataxia, and signs of cerebral edema. In the latter instance, there may be bulging of the anterior fontanel and spreading of the sutures in infants, and papilledema in older patients. Persistent vomiting and fever are very frequent. Nonetheless, the spectrum of illness manifest by patients with encephalitis is extraordinarily broad. Patients may have only headache, with or without fever, lasting for less than a day, and still have serologic evidence of arbovirus infection. Conversely, with infection due to the same virus, some patients manifest a fulminant course of encephalitis with rapid onset of seizures and death. The etiology is rarely suggested by the clinical syndrome, except in the case of herpes simplex encephalitis, in which a sudden onset of abnormal behavior and disorientation is followed by focal neurologic signs in patients with high fever. When skin and/or mucous membrane herpetic lesions are present, the diagnosis is often easier. However, arbovirus encephalitis may present in a similar fashion, even including temporal lobe localization of the infectious process.[19,68]

Although a fulminant course is possible, subacute progressive signs of encephalopathy are more characteristic of measles or rubella subacute sclerosing panencephalitis.

Diagnosis

Encephalitis is usually suggested by the demonstration of abnormal neurologic signs in a patient with fever. Electroencephalographic features include generalized dysrhythmias, but these changes can also be extremely focal in nature. The CSF may be normal in up to 25% of patients.[127] In those patients with abnormal spinal fluid, lymphocytic pleocytosis (generally under 1000 cells/mm^3) is most often seen; however, polymorphonuclear leukocytosis and red blood cells may also be noted. The protein concentration is mildly elevated in many of these cases, and the CSF glucose concentration normal. In exceptional cases of herpes simplex and enterovirus infection, hypoglycorrhachia may be seen. Thus, the CSF is often suggestive, but rarely diagnostic of this condition. Because of the importance of establishing an etiologic diagnosis for the purposes of treatment and prognosis, it is important to go several steps further in unraveling the cause of infection in these cases. Examination of CSF for antibody against suspected viral agents may be useful. A serum:CSF ratio of 32 or less was seen in 7/22 cases with viral encephalitis.[131] Similarly, CSF antibodies were encountered in 9/13 cases 2 weeks after the onset of encephalitis,[32] and CSF IgM elevations above 1 mg/100 ml were noted in 24/40 patients with arbovirus encephalitis.[65]

CT often shows areas of uneven density, but rarely provides a specific diagnosis. It is important to obtain this test, however, to rule out conditions that may readily be confused with encephalitis (Table 9–16). The diagnoses of several of these, including brain abscess, tuberculoma, infarction, and hemorrhage, have been greatly facilitated by this diagnostic procedure. The usual course of events after encountering a patient with an acute onset of encephalitic signs is to obtain a CT scan first and then proceed with a diagnostic lumbar puncture, after increased intracranial pressure is ruled out (and the presence of a space-occupying intracerebral lesion is also shown to be unlikely).

TABLE 9–16. Differential Diagnosis of Infectious Encephalitis

Brain abscess
Brain tumor
Cerebral infarction
Endocarditis
Intracranial or intracerebral hemorrhage
Multiple sclerosis
Tuberculous meningitis
Cerebritis
Reye syndrome
Arterial-venous malformation
Toxic encephalitis

Brain biopsy is also an important consideration in some patients with encephalitis. As it often turns out, the etiologic diagnosis is not apparent in as many as one-half of these patients. If herpes simplex is considered, or if the patient could possibly have a subdural, epidural, vascular, or neoplastic lesion, it is evident that exploration and brain biopsy may be extremely useful. It may also be useful in patients who may have fungal or mycobacterial causes of encephalitis that require specific therapy. The risks of brain biopsy are least in the hands of those experienced in the procedure, and include bleeding and seizures in a small number of patients. When the biopsy procedure is performed through a craniotomy, it may be therapeutic by relieving some of the intracranial pressure.

Treatment

The treatment of viral encephalitis is mainly supportive, with the exception of herpes simplex virus infection or some of the rare treatable conditions outlined in Table 9–15. Patients with encephalitis require careful attention to their cardiorespiratory status, seizure control, and fluid balance. The latter may be perturbed because of inappropriate ADH secretion, impaired intake, and vomiting. Ventilatory support and oxygenation should be optimal, since recovery will depend as much on effective oxygenation and nutrition of the brain as on any other factors.

Prognosis

The prognosis of encephalitis is extremely variable. Mortality may be as high as 67% with herpes simplex encephalitis and 12% with other causes.[127] In many series, survival is tainted by serious neurologic sequelae in up to 30–50% of survivors. These include convulsions, seizure disorders, aphasias, spastic quadriplegia, attention-deficit disorders, motor disorders, retardation, personality disorders, and blindness. Patients with convulsions and coma at the onset of their illness seem to have the worst prognosis. When intracranial pressure or deep coma ensues for longer than 2 days, the outcome is also guarded.[154] It is not always as simple as that, however, and experiences with patients who awaken after several days (and even weeks) in deep coma, with almost miraculous recovery of function, argue against abandoning hope for high-quality survival in this condition.

Herpes Simplex Encephalitis

Epidemiology/Pathogenesis

Herpes simplex virus type 1 is the commonest cause of sporadic encephalitis. Unfortunately, this infection is extremely serious and difficult to diagnose. Moreover, it strikes young and old alike, with little warning.

Although fewer than 500 cases/year are estimated to occur in the United States, the exact figure cannot easily be determined because of the difficulty of establishing a diagnosis. Herpes encephalitis may be part of disseminated herpetic infection in newborns (Chapter 3), or may be localized only in the brain. In older patients, most of whom are completely normal immunologically, the virus invades the brain with no other manifestations. Approximately one-third of patients may have some cutaneous or mucous membrane lesions due to herpes infection as well. The virus is thought to reach the brain by direct extension through the cribriform plate and into the frontotemporal cerebral tissue.[52] It may also infect the brain by the hematogenous route, as suggested by the association of encephalitis with disseminated disease. Occasionally, second episodes of the disease may be seen, which probably represent reactivation of latent infection.[53]

Etiology

The vast majority of encephalitis cases due to herpes simplex virus are caused by type 1; however, in the newborn, type 2 is often responsible.[171] Generally, primary type 2 herpes simplex infection in patients beyond the newborn age is associated with an aseptic meningitis or meningoencephalitis syndrome, which is milder in course and outcome.[84]

Clinical Manifestations

The most frequent presentation of herpes encephalitis beyond the newborn period is fever with a sudden change in mentation. This may be abnormal behavior, disorientation, visual or other sensory aura, or paraesthesias. Signs may be referable to occipital[15], temporal or brain stem localization.[197] In some cases, the patient is initially thought to have toxic encephalopathy; however, it should be remembered that high fever is rarely a feature of that condition. A history of a cutaneous or mucous membrane lesion should also raise suspicion of herpes. Although variable, the course often progresses to a stage where focal neurologic signs become evident. This may be unilateral weakness or paralysis, or a focal seizure. Headache, vomiting, and altered states of consciousness are also frequently encountered.

Diagnosis

This is a diagnosis that must be made as quickly as possible. CT is usually indicated to rule out a brain abscess or other space-occupying lesion that may present similar focal neurologic signs and abnormalities in sensorium, as well as seizures. Although areas of decreased attenuation may be present, it should be remembered that the CT scan is not used to confirm the diagnosis of herpes simplex, but rather to exclude conditions that may mimic this infection.[124] The next most useful test is the lumbar puncture, since the CSF is often abnormal and confirms the presence of meningoencephalitis in approximately 80% of cases.[244] A small number of red blood cells may be seen in this fluid, as may a predominance of polymorphonuclear leukocytes. More characteristic is predominance of lymphocytes with fewer than 1000 total white blood cells/mm^3; a normal glucose concentration, and a slightly elevated protein.[127] Occasionally, hypoglycorrhachia may be noted. The most critical test in the diagnosis is an electroencephalogram, which will often demonstrate fast and slow waves in the temporal leads.[244]

There is some controversy about the next appropriate step in such patients. Some believe that the febrile child with the CSF findings described above, negative bacterial cultures, and focal neurologic signs should be presumed to have herpes simplex encephalitis, if the electroencephalogram is compatible. This seems a reasonable approach, particularly when herpetiform skin or mucous membrane lesions are also present. When the course is atypical, or other diagnoses are possible (suggested by travel to areas endemic for coccidioidomycosis, or by changes that suggest cryptococcosis, contact with tuberculosis, etc.), brain biopsy should be carried out.[242] Biopsy should also be done when the electroencephalogram and other signs are not typical. This is because specific antiviral treatment is available, but it is not free of side effects. Moreover, missing another treatable cause of encephalitis, albeit rare, can be disastrous. This is illustrated by cases of cryptococcosis, aspergillosis, and, occasionally, subdural empyema, that may be missed by other diagnostic procedures, including the CT scan. The morbidity associated with brain biopsy in such patients is slight in experienced hands, with only 2/200 cases included in the United States Herpes Simplex Collaborative Antiviral Study Program experiencing bleeding.[244] Biopsy material should be examined by histopathological, immunofluorescence, electron microscopic (Fig. 9–3), and viral culture techniques.[172] Unfortunately, the brain biopsy may be falsely negative in rare cases.[134]

The differential diagnosis in cases of herpes simplex encephalitis should include brain abscess, tumor, Reye syndrome, intoxication, toxoplasmosis, cryptococcosis, tuberculosis, arterial-venous malformation, and Epstein-Barr virus, influenza, coxsackie virus, mumps, lymphocytic choriomeningitis and arbovirus encephalitides.[68]

Treatment/Prognosis

The treatment of herpes simplex encephalitis requires management of increased intracranial pressure, seizures, blood pressure, and cardiorespiratory dysfunction. Specific antiviral therapy consists of vidarabine or acyclovir, administered in doses of 15 mg/kg/day for approximately 7–10 days. Vidarabine reduced mortality from 30% to 9% in patients under

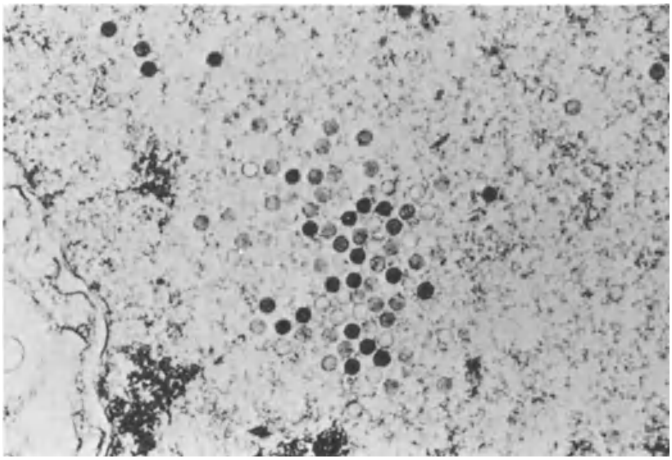

Figure 9–3. Herpes simplex virus in brain tissue of patient with encephalitis. (Courtesy of Dr. G. Altshuler.)

30 years of age treated before the onset of coma.[243] The side effects of vidarabine include nonspecific rash and inappropriate ADH secretion and fluid retention. Acyclovir is also highly effective, but can be caustic to subcutaneous tissues if it is extravasated and may occasionally be associated with nephrotoxicity. Although both therapies are fairly effective when instituted before coma or prolonged seizure activity develops, neither will be consistently associated with a beneficial outcome if the treatment is begun at a later stage. Results of such therapeutic intervention indicate that mortality should be reduced to less than 20%, and the patient should be relatively free of permanent sequelae in up to 70% of cases. If treatment is delayed, the prognosis is much graver, with 30–50% mortality and neurologic sequelae in up to 90% of survivors.[243]

Amebic Meningoencephalitis

Epidemiology/Pathogenesis/Etiology

This is not a common condition, as less than 130 cases have been reported.[220] Two general types of amebic meningoencephalitis exist. In one, due to *Naegleria fowleri,* infection is usually associated with exposure to fresh water in warm climates, and the clinical course is fulminant, with death within 5 days. Naegleria infection is predominantly seen in the southern United States and has also been reported in Belgium and Australia. These free-living amoebae invade the brain via the olfactory epithelium and induce considerable hemorrhagic necrosis of brain matter in the olfactory, frontal, and cerebellar tissues.

The second type is due to the Acanthamoeba-Hartmanella genus, and is more insidious in onset, with death ensuing after a more chronic course. There is no history of fresh-water exposure and the patients are often debilitated and immunosuppressed.[115] These amoebae can occasionally disseminate hematogenously to skin, eye, and other organs.

Clinical Manifestations

Naegleria meningoencephalitis is characterized by the sudden onset of fever, vomiting, headache, and signs of meningitis, encephalitis, or both. Myocarditis has also been described in association with these findings, although the organisms have not been demonstrated in myocardial tissue.[220] Signs of brain abscess may also be present in some patients. There is often rapid progression from fever and early signs of meningitis, encephalitis, or meningoencephalitis to coma and seizures. Infections due to Acanthamoeba are more insidious in onset and chronic in course.

Diagnosis

The CSF demonstrates pleocytosis (predominantly polymorphonuclear), increased protein concentration, and a normal or decreased glucose level. Motile amoebae (8–15 μm) can sometimes be seen in wet-mount preparations of the CSF. Occasionally, biopsy of brain tissue is required for demonstration of the causative organism.

Treatment

Almost all cases of amebic meningoencephalitis have been fatal. In the few survivors, early diagnosis, intensive care, and early treatment with amphotericin B seemed critical. A recent survivor received amphotericin B plus rifampin plus miconazole; the miconazole was given intraventricularly and intravenously.[210] These organisms are also sensitive to tetracycline in vitro;[227] however, mouse protection studies have shown that only amphotericin B may be effective, and then only to a level of 60%.[220]

Prognosis

Death rapidly ensues within 3–5 days after onset of symptoms in patients with Naegleria meningoencephalitis. Those infected with Acanthamoeba have a more chronic course, although many die as well.[240] Effective management of this condition will depend on the development of better drugs and on increased awareness of the condition and means for its early diagnosis.

Rabies

Rabies should be considered in every case of encephalopathy in which the etiologic diagnosis is obscure. Although the incubation period is usually 1–2 months, much longer intervals between exposure to rabid animals and development of the disease have been recorded. There are two major forms of rabies, the paralytic and furious form.[60] In the paralytic form, the medulla, spinal cord, and spinal nerves are principally involved and the patient is often unable to speak because of laryngeal paralysis. In the furious form, the brain stem, cranial nerves, and higher centers are involved and the patient often convulses and has severe hydrophobic spasms.

Prodromal symptoms include fever, headache, and paresthesias at the site of the bite, and are usually followed by pain, flaccid paralysis, and sensory abnormalities; these latter manifestations are most severe in or, even confined to, the bitten extremity. Sensory abnormalities are helpful in differentiating this disease from poliomyelitis and enterovirus poliomyelitis-like syndromes. Patients may also have transverse myelitis and Guillain-Barré syndrome.[60]

The diagnosis of rabies is confirmed by appropriate history, examination of the biting animal, or examination of corneal scrapings or brain biopsy material in the affected patients. Light microscopy should not be relied on to make this diagnosis,[50] since the fluorescent antibody technique is much more specific and accurate.

The treatment of rabies encephalitis is difficult since convulsions and paralysis of the respiratory muscles usually lead to death. There have been a few survivors, however, and intensive respiratory care and muscle relaxant therapy are indicated in all cases.[93] Prevention of rabies and postexposure management are discussed in Chapter 1.

Brain Abscess

Pathogenesis

With refinements in diagnostic techniques, brain abscesses are being recognized at earlier stages in their evolution. The pathogenesis of brain abscess in many situations represents direct spread of infection from a contiguous site, such as sinus, middle ear, or meninges. Cerebritis may be an intermediate step in this process,[146] which seems particularly prevalent with Staphylococcus and Listeria infections.[236] The objective is to establish these diagnoses as early as possible in the hope of prevention of brain abscess and its consequences. The most frequent predisposing factors in North America include congenital heart disease, otitic and sinus infections, closed head injury, sepsis and meningitis, immune deficiencies, dental infections and surgery,[79] and esophageal dilatation.[136] Cystic fibrosis may also be present in a small number of patients.[6,79] Traumatic head injury may be relatively minor, such as pencil tip puncture wounds of the upper eyelid, but may result in brain abscess.[82] In China, the most frequent predisposing factor for the development of brain abscess is chronic middle ear infection.[249]

Etiology

In general, brain abscesses are due to bacterial causes that reflect the flora of the upper respiratory tract (Table 9–17). A polymicrobial etiology is described in at least 30% of cases, and, with careful specimen collection and culture methods, anaerobic bacteria are isolated in almost all cases associated with contiguous spread from middle ear, sinuses, and dental sites. Sometimes the flora may suggest the predisposing factor. This is illustrated by the association of Eikenella brain abscess with a dental focus or drug abuse.[30] Brain abscesses may also be due to *M. tuberculosis,*[230] *Histoplasma capsulatum, Aspergillus fumigatus,* Curvularia infections,[85] *Toxoplasma gondii,* and several other causes, particularly in immunocompomised patients.[11]

Headache and seizures are the most frequent presenting signs of cerebral cysticercosis, due to *Taenia solium.*[186] In such cases, CT and serologic tests (indirect hemagglutination) are useful diagnostically.[148] Praziquantel is effective treatment and surgical excision of cysts is now rarely required.

TABLE 9–17. Etiology of Brain Abscess

Aerobic and anaerobic streptococcal infections (including *S. pneumoniae*)
Staphylococcus *sp.*
Haemophilus *sp.*
Bacteroides *sp.*
Diphtheroids
E. coli
Proteus
Citrobacter
Listeria[58]
Eikenella
M. tuberculosis[230]
Nocardia caviae[26]
Aspergillosis[11]
Blastomyces[138]
Mucor[100]
(Cladosporium *sp.*)[202]
Toxoplasma[69]
Trichinella

Echinococcus can also present this way; mebendazole is useful therapy but surgery may be needed.[182]

Clinical Manifestations

As with other CNS infections, vomiting, headache, lethargy, fever, and seizures are prominent features in the presentations of these illnesses. Abnormal mental status, signs of increased intracranial pressure, and cranial neuropathies may also be present at the time of diagnosis. Hydrocephalus may be a presenting manifestation of brain abscess in newborns.

Diagnosis

The diagnosis of brain abscess has been revolutionized by the development of CT (Fig. 9–4). Although some studies may be falsely negative at an early stage, the resolving powers of these new tests are rapidly improving and should facilitate the diagnosis in almost all cases.[230] In general, suspicion of a brain abscess should prompt this test before lumbar puncture, because of the risk of herniation. In one series, the mortality without clinical evidence of herniation in 297 cases was less than 9%, whereas 64% of the 103 patients with herniation died.[249]

The CSF findings in patients with brain abscess may be pyogenic, with positive cultures obtained in up to 30% of cases. Approximately half of the patients, however, will have only moderate degrees of pleocytosis, slightly low or normal glucose concentrations, and normal or elevated protein concentrations. Approximately 15% of spinal fluids will be completely normal. Patients with an open fontanel are at lowest risk of herniation after a lumbar puncture, even though brain abscess may be present. Patients with evidence of brain abscess and papilledema should be

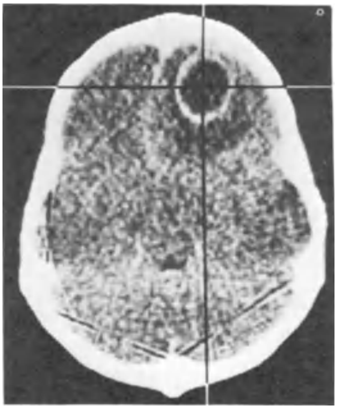

Figure 9–4. Brain abscess demonstrated by CT. (Courtesy of Dr. P. Barnes.)

taken to the operating room for aspiration and drainage of the lesion, before lumbar puncture is performed.

Treatment

The most important aspect of treatment in brain abscess is drainage, although successful medical management has been reported.[194] It is likely these patients had cerebritis, rather than true abscesses; however, differentiating these two conditions pre-operatively can be difficult. Although drainage may be performed by aspiration or excision, repeated aspirations may be necessary if the former course is chosen. Although the same mortality figures have been noted with each of these methods, up to 25% of patients require three aspirations.[79] Unless contraindicated, aspiration and drainage should be carried out immediately on suspicion of diagnosis for two reasons. The first is the marked influence effective drainage has an outcome. The second is the diverse bacterial etiology of this condition. Antibiotics should be tailored to meet the specific microbial causes of brain abscess and should be administered for at least 4 weeks after bacteriologic sterilization and/or marked clinical and inflammatory improvement has been noted. Continued use of a broad initial antibiotic regimen for this period of time will usually be associated with toxicity. If surgery is contraindicated, or when cerebritis is strongly suggested, a 3–5 day trial of medical therapy may be useful. In the absence of clinical improvement, surgery should be reconsidered.

Several antibiotic programs can be used in order to cover the expected causes of brain abscess (Table 9–18). These antibiotics should be started in the operating room, immediately after appropriate specimens of the abscess material are obtained. Penicillin and chloramphenicol have been a favorite combination and cover much of the flora expected. However, because of chloramphenicol's rare but serious toxicities, some prefer to use other combinations, such as oxacillin, metronidazole, and moxalactam

Table 9–18. Treatment of Brain Abscess

SURGICAL DRAINAGE *plus*
Penicillin 300,000 units/kg/day, divided q 4 h IV
plus
Chloramphenicol 75 mg/kg/day, divided q 6 h, IV or PO
or
Oxacillin 200 mg/kg/day, divided q 6 h IV
plus
Metronidazole 30 mg/kg/day, divided q 8 h IV or PO
plus
Moxalactam 200 mg/kg/day, divided q 6 h IV

(Table 9–18). All of these antibiotics penetrate brain abscesses well, although organisms may persist despite appropriate antibiotic therapy.[18] This, again, emphasizes the need for effective drainage.

Prognosis

The mortality associated with brain abscess has been markedly reduced to 14% in children since 1970,[79] and to less than 10% in most recent years. Most of the mortality and serious morbidity are seen in patients who present with coma or who develop hemorrhage or serious neurologic signs early in their course. Deep-seated infections that increase the risks of surgery are also associated with a poor outcome. Although 50% of survivors of brain abscesses will be completely normal, up to 25% may have persistent seizures and major neurologic sequelae.

Subdural/Epidural Abscess

Subdural empyemas are most commonly associated with infection, trauma, or surgery of paranasal sinuses, mastoids, and middle ear, but can also occur in the acute stage of meningitis.[217] Collections of fluid in the subdural space after the fifth day or so of meningitis are usually sterile and their management should be conservative.

Epidural abscesses are somewhat different, since predisposing factors more commonly include trauma, skin infections, and sepsis.[123] Paraspinal epidural abscesses have occasionally been reported after lumbar puncture.[16] Epidural abscess is also different from subdural empyema because the most common etiology is *Staphylococcus aureus*, whereas Haemophilus, pneumococcus and, rarely, meningococcus cause subdural empyema in patients with meningitis. Tuberculosis, hydatid cyst, and unusual bacteria and fungi (e.g., Aspergillus)[31] may also cause abscesses in both locations, particularly in drug abusers. Both spinal and epidural infections occur at all ages, even in newborns.[20]

Clinical Manifestations/Diagnosis

The clinical manifestations of subdural/epidural abscesses are usually referable to the site of the infection. Patients with paraspinal epidural empyema have localized pain, skin erythema, back stiffness, and fever.[70] Neurologic signs may be present if there is neural compression. Transillumination, CT (Figure 9–5),[56] and sonography are all useful diagnostic tools, but confirmation depends on needle aspiration with appropriate microscopic examinations and culture.

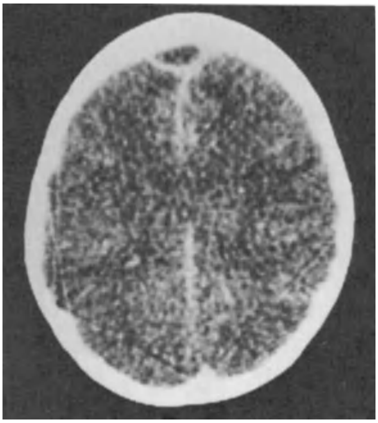

Figure 9–5. Epidural abscess demonstrated by CT. (Courtesy of Dr. P. Barnes.)

Management

Management of these empyemas consists of drainage as early as possible. The prognosis in such cases is excellent.[113] Treatment begun after neurologic signs develop is more commonly followed by long-term sequelae. For epidural lesions, antibiotic therapy, as an adjunct to drainage, should intially include antistaphylococcal medication, as well as antibiotics directed against the common causes of bacterial meningitis.[70] When tuberculosis is suspected, antituberculous drugs should also be included in the initial regimen. Antibiotic therapy should then be individualized, based on the microbiologic diagnosis. Therapy is rarely required for longer than 2 weeks, contingent on the use of appropriate drainage. Exceptions include tuberculosis and osteomyelitis of the vertebral column.

Tetanus

Epidemiology

Tetanus is rare in developed countries; however, approximately a half million cases are still seen worldwide. The disease is preventable (Chapter 1), yet continues to plague nations where children are underimmunized and hygienic practices are substandard. The majority of cases are acquired from contaminated wounds or during birth. The mortality of this dreaded disease still exceeds 50%.

Etiology

This is a neurologic manifestation of infection due to *Clostridium tetani* (Fig. 9–6), which produces a toxin, tetanospasmin, responsible for many of the manifestations of the illness.

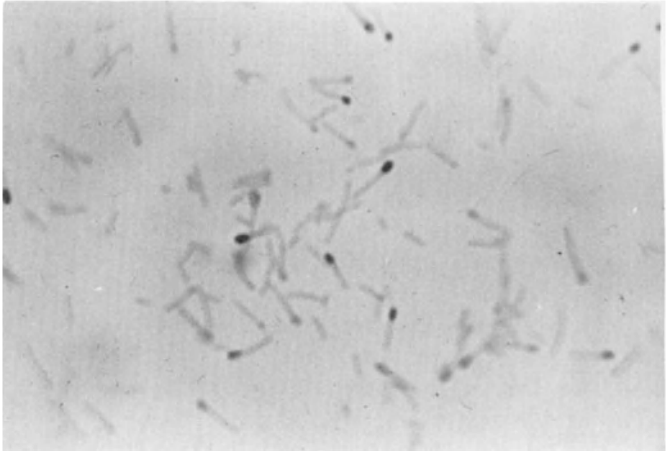

Figure 9–6. *Clostridium tetani.*

Clinical Manifestations

There are several different forms of tetanus, depending on the site of the wound and on the amount of toxin absorbed. Characteristically, the disease is manifest by tonic-clonic muscular contractions, with difficulty in swallowing and spasms of the muscles of the neck and face. The incubation period varies from 4 days to 3 weeks. The term "lockjaw" is used to describe the patient with severe trismus of the masseter muscles. Opisthotonos and seizures may also be seen. Spasms of the abdominal and paraspinal muscles are extremely distressing and may produce abnormal postures, severe back pain, and rigidity. Some of these manifestations may also be seen with strychnine poisoning, phenothiazine ingestion, hypocalcemic tetany, and hysteria.

When acquired in the newborn, tetanus is characterized by a poor suck reflex, increased tone, and spasms.[203] Cephalic tetanus is a rare form of disease that occurs after contaminated injury in the head and neck region. Because of the proximity to the CNS and cranial nerves, the incubation period is extremely short (1–2 days). Cranial nerves are involved early, with specific neurologic dysfunctions and sympathetic nervous system abnormalities. This has been described after head trauma, in the presence of nasal foreign bodies,[206] and after chronic ear infection.[80]

Diagnosis

History of inadequate immunization, contaminated wounds, and a typical clinical picture are diagnostic. Occasionally, *Clostridium tetani* can be grown from specimens of the wound.

Treatment

Control of neurologic symptoms and their effects on breathing and metabolic functions are of first priority. Thus, adequate ventilation and sedation are essential. The patient responds to a variety of stimuli with severe spasms and even seizures. Therefore, a quiet, dark environment is useful. Sedation can be accomplished with barbiturates, diazepam, or in extreme circumstances, by anesthetizing or curarizing the patient. It should be remembered that these procedures accentuate the autonomic dysfunction characteristic of this disease. Meticulous care of such dysfunction and metabolic abnormalities may represent the difference between life and death in these severely ill patients. Neuromuscular blockade and positive pressure ventilation have been lifesaving in newborns with tetanus.[2]

The wound should be packed open and debrided frequently. Tetanus immune globulin should be infiltrated around the wound and given systemically (Chapter 1). Penicillin should also be administered. Although controversial, the use of intrathecal tetanus immune globulin may be beneficial in the first 24 h after diagnosis.[98]

Remember that the dose of tetanus toxin causing disease is usually much smaller than that required for adequate immunization. Therefore, tetanus vaccination should be instituted at the same time, although in the opposite arm, as administration of tetanus immune globulin, and the vaccination series completed during convalescence. Neonatal tetanus may be prevented by hygienic practices at the time of delivery and by adequate maternal immunization.[63] This consists of two doses of alum-precipitated tetanus toxoid, given either during pregnancy or up to 4 years previously.

Botulism

Etiology/Pathogenesis

Botulism reflects the neurologic effects of toxin elaborated by various types of *Clostridium botulinum* (most disease is due to types a, b, and e). Food is the usual source, although the bacteria may also be inoculated into wounds, particularly compound fractures.[125]

Clinical Manifestations

The incubation period of botulism after food ingestion is usually 6 h to 8 days; however, the incubation period may be prolonged to 3 weeks after wound infection. Initially, patients develop weakness, pain on swallowing, dry mouth, diplopia, and dysarthria.[111] Many patients also have nausea, vomiting, abdominal pain, and diarrhea. Lethargy, weakness, dilated pupils, ptosis, and progression of these signs to respiratory failure are typical features. Pulmonary involvement is almost entirely due to weakness of respiratory muscles. Prognosis after recovery is excellent.[208]

Since fever is seldom present, the differential diagnosis includes many noninfectious conditions, including Guillain-Barré syndrome, intoxications, cerebrovascular accidents, myaesthenia, tick paralysis, and several infections, including those of the CNS.

Diagnosis

The diagnosis is confirmed by demonstration of botulinum toxin in the patient's serum. This is done by a neutralization assay in mice. *Clostridium botulinum* can also be cultured from wounds, and, occasionally, from food or gastrointestinal contents. Demonstration of toxin or bacteria is diagnostic. Electromyograms are also useful, since demonstration of decreased amplitude and facilitation of muscle action potential after tetanic stimulation are characteristic of botulism. The CSF protein concentration may be mildly elevated, but this is not diagnostic.

Therapy

Specialized nursing care and respiratory support are often required. Since weakness may involve all systems, patients with botulism may also need urinary catheterization, disimpaction, and tube feeding. Specific antitoxin should be administered (Chapter 1), as well as penicillin. Botulism antitoxin can neutralize circulating toxin but has no effect on tissue and cell-bound material. If wound infection is involved, wide debridement and drainage of purulent material are indicated. Aminoglycosides should be avoided, since they may potentiate the effects of botulinum toxin.[205]

Infant Botulism

A variant of botulism is seen in newborns and young infants. It is characterized by hypotonia, constipation, failure to thrive, and, in some circumstances, sudden infant death syndrome.[226] The disease has been associated with the ingestion of honey[5] and with the use of formulas, rather than human milk.[4] Treatment, as for other forms of botulism, depends on aggressive and careful supportive care, particularly for cardiorespiratory functions. Penicillin is used to sterilize the bowel of *C. botulinum,* although its effect is not dramatic.

The prognosis in botulism depends on early diagnosis and aggressive management of neuromuscular weakness and its complications. The disease is self-limited if these complications can be overcome.

Reye Syndrome

The cause of Reye syndrome is unknown, but it is considered related to infection because of its known occurrence during convalescence from viral illnesses.[222] The most frequently associated viruses are varicella and influenza (especially influenza B). Children with vomiting, hepatic dysfunction, and minimal neurologic impairment after upper respiratory or varicella infection may have this condition.[143] Aspirin therapy has also been linked to the pathogenesis of this syndrome.[251]

The syndrome is manifest by vomiting, abnormal behavior, lethargy, and seizures.[61] Most affected children are between 5 and 15 years of age. The viral infection is thought to trigger an aberrant immune response, resulting in encephalopathy with fatty degeneration of the viscera.

Laboratory findings include elevated concentrations of serum transaminases and ammonia, and a prolonged prothrombin time. Hypoglycemia, acidemia, and azotemia may also be present. Diverse clinical and laboratory features of CNS, hepatic, and renal dysfunction may also be present.

Supportive therapy is directed at respiratory assistance, management of intracranial hypertension, and correcting fluid and metabolic derangements. Definitive prevention and therapy await elucidation of the cause and/or pathogenesis of this unusual condition.

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10

Genitourinary Infections

Urinary Tract Infections

Urinary tract infections include inflammatory changes in the urethra, bladder, ureters, and kidneys; often these anatomic divisions are crossed. Since it is frequently impossible to differentiate lower from upper urinary tract infections in children, the following discussion is applicable to both.

Epidemiology/Pathogenesis

Any condition that interferes with urinary outflow, or is associated with some retention of urine in the bladder, such as the presence of indwelling urinary catheters, neurogenic bladder syndromes and congenital and acquired obstructions,[91] predisposes to urinary tract infection. Trauma, sexual intercourse,[131] constipation, Hirschsprung disease, and infections related to the use of catheters may also be significant. Even pinworm infection has been implicated in some young girls.[99]

Urinary tract infections are seen in approximately 1% of schoolgirls and in 0.03% of schoolboys.[100,101,103] The frequency in girls will increase with sexual activity. Urinary tract infections in boys are more often associated with underlying renal structural abnormalities.[24,75] Newborns are different, in that most of their urinary tract infections are acquired by the hematogenous route. In the first 3 months of life 75% of infections are seen in boys;[60] in contrast, only 11% of cases occur in boys between the ages of 3 and 8 months. In boys, 95% of the infections in one study occurred in uncircumcised patients.[60]

The gastrointestinal tract serves as the major reservoir for the bacteria causing urinary tract infection.[70] The distal urethra and periurethral area are also colonized by enteric bacteria,[54] which may be the reason for the association of acute urethral syndrome, cystitis, and urinary tract infection with sexual activity, masturbation, and trauma to the lower urinary tract. This should be kept in mind whenever catheterization is considered.

Several other host factors are important in the pathogenesis of urinary tract infections as well. The longer urethra and prostatic secretions may be protective in males;[41] however, bladder defense mechanisms in both sexes may be overcome by stasis, obstruction, abnormal pH, and dysfunction of phagocytes and local antibody, particularly IgA.[187]

Invading microorganisms also have features that determine their involvement in urinary tract infection. These include the capacity to adhere to bladder mucosa through a reaction between bacterial fimbriae and receptor carbohydrates on epithelial cell walls.[200] Approximately 70% of urinary tract infections are also due to five K antigen types of *Escherichia coli*[89,90] and 80% of these strains belong to eight O antigen groups.[108] *E. coli* associated with symptomatic urinary tract infections are less sensitive to the bactericidal effect of normal serum, are less well opsonized, and have thinner capsules.[12]

The pathology of cystitis is characterized by swelling of the bladder mucosa with disturbance of function of the uretero-vesical and, occasionally, the vesico-urethral junctions. This is reflected radiographically by reflux of urine from the bladder into the ureter and by residual urine in the bladder after voiding. It should be remembered that these are usually transient effects. In fact, the temptation to diagnose bladder neck obstruction, meatal stenosis, or vesico-ureteral reflux should be resisted until several months after the acute infection has been controlled and radiographic examinations are repeated. Normal bladder neck diameters vary from 3 to 19 mm, distal urethral segments from 2 to 8 mm, and meatal diameters from 2 to 7 mm.[157]

When the kidney is infected, microscopic changes include infiltration by mononuclear and polymorphonuclear leukocytes, edema, and parenchymal necrosis, which is often focal in nature and reversible. Gross alterations, including renal atrophy, calyceal destruction, distortion, and fibrosis, may be seen with repeated infection or with inadequately treated acute pyelonephritis. It is these changes that must be watched most closely, since they correlate with decreased renal growth and predisposition to recurrent infection. The pathogenesis of these changes relates in part to the persistence of bacterial antigen in kidney tissue, bacterial toxins, inflammatory responses to the acute infection,[61] and antibody produced against kidney antigens.[145] The resultant injury often adds to prior conditions that favor the presence of residual urine, obstruction, and other abnormalities of renal flow.[199] These changes may be reflected by abnormal renal function, hypertension and, in some cases, by actual destruction of large portions of the kidney and its collecting system.

Pathophysiologic changes in patients with kidney infections include an inability to concentrate urine above 800 mOsm/liter after 14 h of fluid deprivation, and an elevation of erythrocyte sedimentation rate above 25 mm/h.[144]

Etiology

Most urinary tract infections are caused by *E. coli.* This is true for more than 90% of cases of acute bacterial cystitis,[193] as well as more than 90% of cases of pyelonephritis in girls and 65% in boys.[24] Other enteric bacterial causes are also common (Table 10–1). Morganella/Proteus infection is particularly frequent in boys,[96] in whom anomalies of the genitourinary system may also be seen. Staphylococci are being recognized more frequently as causes of urinary tract infection, especially in sexually active individuals, in whom *Staphylococcus saprophyticus* (formerly coagulase-negative *Staphylococcus* or *Staphylococcus epidermidis*) are prevalent.[88] *S. aureus* also causes approximately 1% of urinary tract infections.[32]

Opportunistic bacterial pathogens may also be seen, particularly in patients with indwelling urinary catheters, or other abnormalities of the drainage system. In such cases, fungal isolates may reflect both local and systemic infection. Repeated cultures of Candida, directly from the kidney or from the upper tract collecting system, suggests the presence of renal candidiasis.[73] Special techniques are often required for the isolation of

TABLE 10–1. Causes of Urinary Tract Infection (UTI)

- Cystitis/Pyelonephritis
  - *Escherichia coli*
  - Enterobacter
  - Klebsiella
  - Morganella/Proteus
  - *Haemophilus influenzae*[67]
  - *Neisseria gonorrhoeae*
  - Anaerobic bacteria[53]
- Opportunistic UTI
  - Pseudomonas
  - Staphylococcus
  - *Candida albicans* or *tropicalis*[47]
  - *Candida (Torulopsis) glabrata*[120]
- Viral Cystitis
  - Adenoviruses 11 and 21[133]
- Granulomatous UTI
  - *Mycobacterium tuberculosis*
  - Schistosoma
  - Toxocara
  - Microfiliariae[87]
  - *Enterobius vermicularis* (pinworms)

opportunists; hence consideration of anaerobes, fastidious bacteria, and fungi is often required for correct etiologic identification.

In some instances, a specific manifestation suggests the etiologic diagnosis. For example, nephrolithiasis is associated with both obstruction and infection. Struvite stones are more commonly infected than those composed of calcium oxalate, and *Proteus mirabilis,* or other urea-splitting organisms (including *Ureaplasma urealyticum*), may be responsible.[138]

Pneumaturia may be a clue to the presence of gas-forming organisms in the urine,[119] or emphysematous cystitis, in which gas-forming microorganisms invade the bladder wall.[194] Causes can include enteric bacteria, Clostridia, or fungi.

Xanthogranulomatous pyelonephritis is a rare chronic renal infection characterized histopathologically by the presence of granulomas, abscesses, and lipid-laden foam cells. Occasionally, this may be a manifestation of chronic granulomatous disease.[86]

When granulomatous histopathologic changes are present in urinary tract tissue, tuberculosis, schistosomiasis, and other parasitic infections should be considered.[87] Rarely, Enterobius (pinworms) or *Ascaris lumbricoides*[82] may obstruct the lower urinary tract and lead to urethritis and cystitis.

Viruses are rare causes of urinary tract infection, even though they have been described in the urine with a variety of systemic viral infections, including hepatitis, mumps, coxsackie, ECHO, and adenovirus.[162] When acute dysuria, hematuria, and low-grade fever are present, adenoviruses type 11 or 21 may be causes of hemorrhagic cystitis.[133]

It should be remembered that noninfectious conditions can also simulate urinary tract infection. For example, use of drugs, such as cyclophosphamide and methenamine mandelate, can produce hematuria and inflammatory cystitis.[151] Trauma, foreign bodies, catheters, and surgery may also cause these signs. Dysuria may occasionally be factitious, as noted in an unusual case caused by urethral compression.[11]

Clinical Manifestations

Diagnosis of cystitis and pyelonephritis is based on clinical, radiographic, and laboratory criteria. In many instances these conditions overlap. Clinical signs most referable to the urethra and bladder include dysuria, frequency, and, occasionally, hematuria, urinary retention, suprapubic pain, urgency, pruritus, and incontinence. High fever, chills, back pain, and costovertebral angle tenderness are more characteristic of kidney infection. With these critera as guidelines, it can be assumed that most newborns and infants probably have infection of several areas of the urinary tract, whereas the acute onset of dysuria, associated with toilet training in girls or with sexual activity in women, usually refers to urethral or bladder infections. Newborns, patients with bacteremia, patients with severe underlying diseases, and those who appear toxic should always be presumed to have pyelonephritis associated with systemic infection until proven otherwise.

Although asymptomatic bacteriuria can be seen in individuals of all ages, the frequency is low. It is worthwhile to consider urinary tract infection in sexually active patients with a variety of genitourinary and abdominal complaints, and in patients of all ages with fever of unknown origin.

The hallmarks of urinary infection in all patients are fever, dysuria, frequency, urgency, and, in younger patients, enuresis. The latter may be nocturnal or daytime, or both, and is highly suggestive of urinary tract infection when this sign recurs after a "dry period." It is not uncommon, however, for these patients to have only dribbling and foul smelling urine without any fever. Patients with infections of the urinary tract may have only fever, or abdominal or back pain, as a presenting feature. Gross hematuria, pyuria or, rarely parasites or gas in the urine can also be seen. Colic, poor feeding, inadequate weight gain, anemia, hyperammonemic encephalopathy,[35] or jaundice in infants may be indicators of urinary tract infection.[130] Signs of chills and severe toxicity suggest the presence of bacteremia and serious gram-negative infection. It is important to watch these patients extremely carefully, as gram-negative sepsis and shock are major risks.

Diagnosis

Urinalysis should be performed whenever there is a suspicion of urinary tract infection. Demonstration of pyuria, hematuria, proteinuria, white blood cell casts, or microorganisms (Fig. 10–1) can be critical toward making a presumptive diagnosis. Culture is essential for confirmation. Both analysis and culture are most reliable when performed on fresh urine obtained by the midstream clean-catch method or by percutaneous aspiration of the bladder. Bladder aspiration should be performed in septic newborns and in other patients in whom antibiotic therapy must be initiated before the urine culture results are available. The procedure is safe in experienced hands, but rare complications, such as bowel perforation or hematoma, can occur.[127] Catheterized specimens are also useful. Specimens obtained from adhesive bags are least reliable in newborns and young infants, and in patients with diarrhea, incontinence, poor hygiene, in menstruating women, in uncircumcised men, and in patients in whom bag has been applied for a considerable period of time.

The technique used for examination of the urine should be standardized. Five milliliters of urine should be centrifuged at approximately 3000 rpm for 3 min and the sediment examined microscopically. More than 20 white blood cells/high power field correlates with a significant bacterial

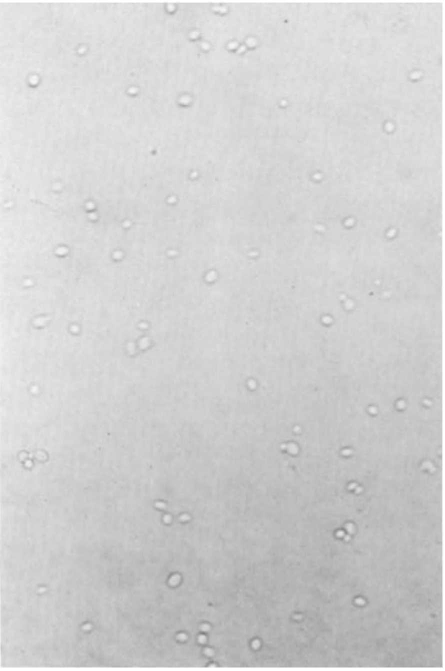


Figure 10–1. Funguria (*Candida glabrata*) demonstrated by light microscopic examination of urine.

count (> 100,000 colonies/ml of urine) in most cases. However, pyuria is also noted in severe dehydration, and associated with drugs, foreign bodies, stones, and after the administration of polio vaccine.[142] Actually, staining is required to differentiate some types of renal epithelial cells from leukocytes, and should be done when neoplasms, parasitic disease, or noninfectious inflammatory conditions are considered.[95] Demonstration of at least 100 bacteria/high power field in the unstained sediment correlates with significant bacteriuria in 90% of cases.[142] When a single type of bacteria is demonstrated by gram stain of the uncentrifuged urine, there is a correlation with significant bacteriuria in about 95% of cases. It should be remembered, however, that a normal urinalysis does not preclude a diagnosis of urinary tract infection.

Urine culture is mandatory in all cases in which the clinical picture and/or urinalysis suggest the presence of urinary tract infection. This diagnosis implies a commitment to radiographic studies, repeated cultures, and long-term followup, and, therefore, should not be made without such a confirmatory step. A culture result indicating > 100,000 colonies of a single organism in a milliliter of urine is the standard for confirming the presence of a bacterial urinary tract infection. When two such cultures are obtained from midstream clean-catch specimens, the diagnosis can be made with more than 95% confidence.[8] When lower concentrations of bacteria are present, one should consider the method of urine collection, and other spurious sources of bacteriuria such as periurethral, vaginal, and preputial lesions in the male, as well as bag specimens in patients with diarrhea should be considered. In other cases, the organism may be fastidious and require a special medium to grow optimally. Yet another explanation is the recent observation that acute urethral syndromes in young women are often associated with coliform infections with bacterial concentrations of 10^2–10^5 bacteria/ml of urine.[168] Occasionally, increased fluid intake with consequent diuresis, the presence of bacteriostatic agents in the urine, extremely acid urine ($pH < 5$), or very dilute urine with a specific gravity of < 1.003 may be responsible for low bacterial counts. Special techniques are required when anaerobes, viruses, fungi, or parasites are suspected as causes.

When urine is obtained for culture directly from the bladder (by suprapubic bladder aspiration or by catheterization), any positive bacterial culture should be considered significant. In the case of catheterization, however, the catheter should not be indwelling and should have been introduced with minimal trauma through a relatively clean urethra and periurethral area. Otherwise, the urine culture results should be interpreted with consideration of skin and periurethral cultures obtained before the introduction of the needle or catheter, respectively. Urine specimens from patients with indwelling urinary catheters are best obtained by direct puncture of the catheter and aspiration with a sterile needle. Urine obtained in this way, or directly from the bladder, should be inoculated undiluted in a volume of approximately 0.1 ml, in order to make the culture result reliable. In contrast, midstream clean-catch urine specimens are cultured in a dilution of 1:1000. If cultures are obtained through a conduit, a double-lumen catheter is recommended to avoid misleading results due to bacterial colonization of the distal third of the conduit. In such cases, $> 1{,}000$ colonies/ml are usually significant.[165] When there is a delay between obtaining the urine specimen and culture, refrigeration at 4°C is recommended. Most enteric bacteria are stable in urine for at lest 24 h at 4°C.[8] If Neisseria or Haemophilus is suspected, however, this may not be appropriate.

Commercial screening tests are often used for detecting bacteriuria in the normal population.[40] Because these tests are associated with false-positive and false-negative results, and often require subjective interpretation, they are best reserved for screening asymptomatic patients.[8,57] All positive results should be confirmed by traditional bacterial culture.

In the pediatric population differentiation of upper from lower tract infection has been attempted with little success. Thus, the measurement of urinary lactic acid dehydrogenase is not consistently associated with a specific site of renal infection, as suggested by early studies.[3] The bladder washout technique is most useful, but is not practical in most circumstances.[80] Similarly, measurement of C-reactive protein[81] and excretion of urinary glucosaminidase enzymes are investigational and not currently recommended.[141] The fluorescent antibody technique has been least useful for differentiating cystitis from pyelonephritis in the pediatric age group, with false-negative results in as many as 20%, and false-positive in up to 52%, of cases.[125] The test has also been tried in patients with neurogenic bladder, without success.[123]

Renal radiography should be performed on most patients with a urinary tract infection. The exceptions include the patient with obvious urethritis, or acute urethral syndrome secondary to trauma, foreign body, or fecal soiling. In patients who have had a bubble bath or sexual intercourse, etc., the examination can be deferred and done only in cases of persistent or recurrent infection. Visualization of the bladder and urethra should be reserved for situations where upper tract abnormalities are found, or when obstructive uropathy is highly suspected.

The most common radiographic abnormality noted in children with urinary infection is vesicoureteral reflux. Since this generally resolves within 6 weeks after infection, the radiograph should be deferred for 6 or more weeks after complete resolution of the clinical and bacterial signs of urinary tract infection. (Ultrasonography can be used early in cases where tumor, obstruction, or hydronephrosis are suggested by the presence of a mass, azotemia, or hypertension). When lower tract lesions are suspected, a voiding cystourethrogram may help visualize the bladder mucosa and vesicoureteral and vesicourethral junctions. A finding of a severe degree of reflux and/or residual urine indicates disease.[193] The criteria employed for the diagnosis of bladder neck obstruction and urethral and meatal stenoses should be rigorous;[157] in actuality, these are rare causes of urinary tract infection. When duplication of the renal pelvis or ureter, or horseshoe kidneys, are present, surgical management is rarely indicated. Neither should the presence of reflux into the urethra or ureters be taken as an indication for surgery or cystoscopy. In fact, there is only a minor role for cystoscopy in the diagnosis of urinary tract infections in children. Indications include a need for urethral calibration, nephrolithiasis, severe reflux where baseline pressure measurements are useful, diverticula, or other localized lesions. Cystoscopy may also be needed to obtain a biopsy in selected cases.

Radionuclide scans, ultrasound, and computerized tomography can often be employed for the diagnosis of reflux, size of the kidneys, and obstructive lesions.[184]

Treatment

Penicillins and sulfonamides have remained the mainstays of treatment for bacterial urinary tract infections. Diuresis is useful in the treatment of acute urinary tract infection as well.[106] Most antimicrobials are excreted in high concentrations in urine.[167] Knowledge of this pharmacokinetic property, and the activities of certain of these drugs at various pH values, is useful (Table 10–2).

Treatment of acute urinary infection with sulfisoxazole or amoxicillin, after appropriate cultures, is followed by repeat clinical and microbiologic examinations in approximately 2–3 days. By this time, the results of in vitro susceptibility studies will be available. Moreover, information on the patient's clinical and microbiologic responses to infection will be available. The patient should be markedly improved and there should be few or no bacteria visible or viable in the urine. If not, poor compliance, bacterial resistance, or an alternative diagnosis (such as an undrained abscess or intermittent obstruction) should be suspected. If resistance is demonstrated in vitro, and microbiologic persistence noted, a more appropriate antimicrobial agent should be chosen. In most cases, in vitro resistance should not prompt a change in chemotherapy if there is clinical and microbiologic improvement, because most of these tests reflect concentrations of the antibiotic in serum, rather than urine.[167]

Urinary tract infection with Candida may be amenable to improvement in underlying factors and to administration of oral 5-fluorocytosine.[195]

The optimal duration of therapy for urinary tract infections is unknown in many cases. What is clear, however, is that single-dose therapy is often associated with failure and early relapse in the pediatric age group,[7] although some success has been reported with a single dose of amikacin in young girls with signs of first lower tract infection.[189] Antimicrobial therapy for 3 days may be adequate for patients with recurrent urinary tract infection and normal radiographic studies,[156] but 6 weeks of therapy is preferred for infants under the age of 6 months, in whom pyelonephritis is likely.[144] In the remaining cases an intermediate duration of 1–2 weeks is most often used. The most important component is followup. This should include a urine culture obtained approximately 1 week after antibiotic therapy is stopped and, thereafter, at 1-month intervals for 3

TABLE 10–2. Effect of Urinary pH on the Activities of Antimicrobials

Drugs	*Optimal pH for Antibacterial Activity*
Erythromycin[204]	Alkaline
Polymyxin B[128]	Alkaline vs. coliforms Acid vs. Pseudomonas
Penicillins	Acid
Methenamine	Acid
Aminoglycosides	Alkaline
Sulfonamides	Alkaline (less soluble in acid)

TABLE 10–3. Oral Antimicrobials Useful for the Prophylaxis of Recurrent Urinary Infections

Drug	*Dose (mg/kg/day)*	*Frequency (doses/day)*
Trimethoprim/sulfamethoxazole	2/10	1–2
Nitrofurantoin	2	1
Trimethoprim	2	1–2
Sulfisoxazole	100	4

months, and at 3-month intervals for the subsequent 18 months. In cases with recurrent infection or pyelonephritis, additonal clinical and microbiologic examinations are recommended twice yearly for 6 years.[102] The exact interval between examinations is not critical, but followup is, because recurrent urinary tract infection is common, often relatively symptomless, and is encountered in approximately 30–40% of children with normal renal systems. Most of these occur within 6 months of the initial infection. Patients with a second recurrence are more likely to have repeated infections thereafter.[23] These infections should be detected early because of the marked effect on renal growth and function noted with untreated urinary tract infections. Even with surgery, progression of urinary tract infection and renal injury is sometimes seen.[190]

When patients develop more than one recurrent urinary tract infection, it is worthwhile to attempt to prevent these by means of continuous antibiotic prophylaxis. Several drugs may be used for this purpose, including trimethoprim,[169] nitrofurantoin,[166] and trimethoprim-sulfamethoxazole[161] (Table 10–3). Trimethoprim-sulfamethoxazole may be used three times/week in adolescent girls.[76] Sulfonamides alone are often associated with the development of bacterial resistance, and are least useful. The duration of prophylaxis should usually be 6 months to 1 year. For underlying genitourinary conditions that are irreversible, such as congenital and acquired urinary abnormalities, nephrolithiasis, etc., prophylaxis should be prolonged. In some of these cases surgery may be indicated. When surgery is performed, chemoprophylaxis may be useful until urinary flow returns to normal.[117]

When is surgery indicated? Most often a combination of medical and surgical therapy is used when a patient has gross structural abnormalities, duplications, valves, ureteroceles, diverticula, bladder exstrophies, or persistent nephrolithiasis,[158] associated with recurrences[79] (Table 10–4). Surgery for vesicoureteral reflux should be reserved for patients with major abnormalities, and for those resistant to medical therapy.[196]

Patients with neurogenic bladders, such as children with meningomyeloceles,[116] are best handled by intermittent urethral catheterization.[29] This approach is preferred over urinary diversion in individuals of all

TABLE 10–4. Indications for Surgical Treatment of Urinary Tract Infection

Progressive pyelonephritis despite appropriate medical therapy
Hydronephrosis
Poor kidney growth
Persistent nephrolithiasis
Major structural anomalies including progressive severe reflux
Severe urethral or meatal stenosis
Presence of a fungus ball

ages, including newborns.[137] Surgical procedures on the urinary tract are often associated with scarring, recurrent infection, obstruction, and disturbance of normal urine flow. A combination of intermittent urethral catheterization and night-time prophylaxis with nitrofurantoin (2 mg/kg) is also useful.[111]

Finally, patients with indwelling urinary catheters are prone to infection as well. When prolonged catheterization is required, systemic antimicrobials or continuous bladder irrigations have been used. These are most useful in the first 4 days. Thereafter, they are commonly associated with emergence of infection due to resistant bacteria.[55] As a consequence, use of closed systems and aseptic techniques, without antibiotic therapy, are indicated in most cases. Treatment of symptomatic urinary tract infections, as they occur in such patients, is then the most useful approach.

5-Fluorocytosine is useful in Candida urinary tract infections because the drug is highly concentrated in urine. Amphotericin B may also be required in renal candidiasis and when candidiasis is part of systemic invasion (Chapter 12). Praziquantel 40 mg/kg in a single dose is effective in the treatment of urinary schistosomiasis,[143] but must be administered before permanent damage to the bladder has taken place.

Patients with fungal (usually Candida) cystitis can be treated with oral 5-fluorocytosine or, if the organisms are resistant, with local irrigations of amphotericin B.[47]

Prognosis

I have spent so much effort describing the pathogenesis, etiology, diagnosis, and treatment of urinary tract infections that the reader might infer that the prognosis is grave. On the contrary, most children with urinary tract infections recover completely[160] and compensatory kidney growth to approximately 99% of the expected kidney surface area occurs, even in patients with focal lesions and reflux during acute infection.[21] Nonetheless, these good results reflect a careful approach to followup and early treatment of recurrent infection. Because of the efficacy of such followup and treatment programs, as well as the use of intermittent catheterization and chemoprophylaxis, a conservative approach is recommended when vesico-urinary reflux is noted, except in its most extreme degree.[1] Newborns with pyelonephritis and those with extensive renal damage and/or structural abnormalities at the time of their first infection have the worst prognosis.

Besides recurrence, the most severe consequences of recurrent urinary tract infection are renal scarring with resultant loss of function, hypertension, and renal insufficiency in a small number of patients. Most commonly, recurrent urinary tract infections plague such patients into adulthood. Then, sexual intercourse is often associated with recurrence. Maternal urinary tract infection during pregnancy increases the risk of premature labor and the birth of infants.[117]

The prognosis for patients with asymptomatic bacterial infection is excellent, so much so that some have questioned the need for treatment.[107] Until more information is available, however, it seems judicious to attempt to eradicate bacteriuria in all individuals in whom it is detected. This also applies to parasitic, fungal, chlamydial, and ureaplasmal infections of the urinary tract. The majority of infants and children with urinary tract infections are otherwise normal, and will tend to outgrow their condition if the problem is carefully managed during early childhood.

Renal Abscess

Epidemiology/Pathogenesis

Renal abscesses are rare in children and very difficult to diagnose. Clues to the pathogenesis and diagnosis include a prior episode of bacteremia or underlying renal abnormalities. The latter may include nephrolithiasis or scarring from previous urinary tract infection. The condition has been described in individuals of most ages, including a newborn with nephrosis.[28]

Etiology

Staphylococcus aureus is the major pathogen causing renal abscess in the pediatric age group; next in frequency are gram-negative bacteria. The mean age of children with staphylococcal renal abscesses is 8 years, and infection is often related to hematogenous spread.[152] In contrast, gram-negative infections, such as those due to *E. coli* or Pseudomonas, are seen in younger children (average age 3 years) and in those with a history of previous urinary tract infection. Occasionally, congenital or parasitic renal cysts may present as a renal abscess, and surgery may be required for both the diagnosis and management.[45]

Clinical Manifestations

These patients may have only fever and nonspecific signs, which makes the diagnosis extremely difficult. Those who exhibit flank pain and tenderness, and those with a palpable mass, are more easily discovered. A more typical presentation, however, is prolonged fever with poorly localized abdominal or back pain.

Diagnosis

Excretory urography with nephrotomography usually provides the most specific diagnosis.[152] Selective arteriography may also be helpful. Computerized tomography (CT) or ultrasonography should be employed before more invasive tests, and can often be used for both diagnosis and to guide percutaneous aspiration.[149] Urine and blood cultures should be obtained in all cases, although they are rarely positive with well-localized renal abscesses. Although the erythrocyte sedimentation rate and white blood cell counts are often elevated, these are nonspecific findings.

Treatment

Medical therapy should be tried in all cases. If a response is not seen within a week of initiation of appropriate antibiotics, a drainage procedure should be considered.[83] This can be done by percutaneous aspiration guided by CT or by an open surgical approach. Occasionally, nephrectomy is required. Antibiotic therapy can be guided by culture results obtained from urine, blood, or directly from the abscess tissue. This is one of the advantages of percutaneous needle aspiration.

If medical therapy is successful without drainage, it should be prolonged for approximately 2 weeks after defervescence and clinical improvement. The prognosis is usually excellent.

Urethritis

Epidemiology/Pathogenesis

Inflammation of the urethral and periurethral tissues may be due to a variety of infectious and noninfectious causes. Both sexually and nonsexually transmitted infections play roles. Urethritis in sexually active patients is most frequently due to gonorrhea and nongonococcal urethritis syndromes,[44] either of which may be associated with vaginitis, balanitis, and conjunctivitis. Sexually transmitted urethritis is most prominent in large urban centers, where activity is concentrated in poor socioeconomic environments. Fecal soiling, use of bubble bath, poor hygiene, foreign bodies, and trauma are important in the pathogenesis of urethritis in infants and children who are not sexually active.

Etiology (Table 10–5)

The most common infectious cause of urethritis in nonsexually active infants and children consists of contamination with coliform bacteria during the early years of toilet-training, but may also be due to pinworms or a combination of these contaminants and chemical or traumatic urethral damage. The former includes bubble baths and other perfumes, and the latter, injuries, foreign bodies, or masturbation.

Sexually transmitted infections in males often manifest first as urethritis, particularly in gonorrheal, chlamydial, and ureaplasmal infections. Nongonococcal urethritis in women has been causally related to infections with *Chlamydia trachomatis* in approximately 30–50% of cases,[172] to *Ureaplasma urealyticum* (T-strain mycoplasma) in up to 70%,[4] and to a combination of these agents in 23%. The remainder of cases of infectious urethritis in postpubescent, sexually active patients may be due to a variety of pathogenic microorganisms including *Trichomonas vaginalis, Candida albicans, acinetobacter,* herpes simplex (predominantly type 2), *Treponema pallidum,* and possibly other bacteria such as staphylococci, Enterobacteriacae, and, occasionally, streptococci. The acute onset of dysuria and frequency in sexually active females is often referred to as the "acute urethral syndrome," when these signs are associated with urine cultures that are either sterile, or considered negative by the usual criteria of > 100,000 colonies/ml. In many of these cases, however, there may be pyuria and fewer than 10^5 bacteria/ml, but these are considered significant. Common causes of this syndrome include coliforms, *Staphylococcus saprophyticus,* and *Chlamydia trachomatis.*[172] *Mycoplasma hominis*[68] and other Mycoplasma species can also be involved.[185] Sexual activity is an important factor in the pathogenesis of this condition.

TABLE 10–5. Infectious Causes of Urethritis

N. gonorrhoeae
Chlamydia trachomatis
Ureaplasma urealyticum
Mycoplasma hominis
Gardnerella vaginalis
Trichomonas vaginalis
Candida albicans
Herpes simplex
Syphilis (*Treponema pallidum*)
Enteric bacteria, including Shigella
Streptococcus sp.
Staphylococcus sp.
Enterobius vermicularis
N. meningitidis[203]

Clinical Manifestations

Urethritis most commonly presents as dysuria, urinary frequency, and urethral discharge. Some hematuria, pyuria, periurethral erythema and swelling, and edema may also be seen.

The differential diagnosis includes erythema-multiforme (Stevens-Johnson syndrome), where the urethral mucosa may be involved, and chemical irritation or allergy to soaps or perfumes. Reiter syndrome denotes the association of nongonococcal urethritis with conjunctivitis and arthritis. The most common cause is *Chlamydia trachomatis.*

Diagnosis

The diagnosis of urethritis is often simplified, if urethral discharge is present. This may be grossly purulent in gonorrhea, or scanty and watery in chlamydia infection. Discharge may be appreciated in some patients only after milking the urethra. In other cases, examination of a swab inserted into the distal third of the urethra may demonstrate the presence of inflammatory cells. The presence of more than four polymorphonuclear leukocytes/high power field of urethral exudate, or more than eight leukocytes/high power field in urine, correlates with an infectious etiology for urethritis.[176] If the gram stain of the urethral discharge in a man demonstrates gram-negative intracellular diplococci, a presumptive diagnosis of gonorrhea can be made and treatment begun. Cultures should be used to confirm the presence of this infection. Smears are less reliable in women, since gram-negative diplococci may be present in the normal flora. When the gram smear is difficult to interpret, or no gram-negative diplococci are seen, nongonococcal urethritis is the most frequent diagnosis in sexually active individuals.

History of sexual practices, exposure to irritants, toilet training, etc., should guide the clinician in the appropriate culture techniques. This is important considering the diverse etiology of urethritis throughout the pediatric age group (Table 10–5). Cultures of urethral discharge and/or urine are indicated in these patients for definition of the exact microbiologic cause. Use of specific techniques such as a wet-mount preparation (or culture for persistent or recurrent cases) for *Trichomonas vaginalis,* growth on selective media for Gardnerella and Sabouraud's dextrose agar for Candida, and viral cultures for herpes simplex may also be indicated.

Treatment

In infants and children who are not sexually active, treatment is directed at the elimination of underlying causes of urethritis. This is fairly simple with respect to the use of bubble baths and soaps, but in regards to instruction in proper hygiene and toilet training techniques, it requires a little more time and education. When there is fecal soiling, a short course of a sulfonamide or amoxicillin should also be prescribed. A single dose can often be used, when coupled with appropriate improvement in personal hygiene.

The treatment of urethritis in sexually active patients is more complicated. If gonorrhea is suspected, therapy and case finding are indicated. Unless the gram smear clearly demonstrates *N. gonorrhoeae*, male patients eight years of age or older with urethritis should be treated with tetracycline, since there is a strong possibility that the patient has nongonococcal urethritis.[4] In such cases, doxycycline 100 mg b.i.d. for 10 days has been found useful for both urethritis in men and the acute urethral syndrome with pyuria in women.[170] Minocycline 100 mg daily, for 7 days, has also been found useful.[15] Case finding and treatment of sexual contacts are also important for nongonococcal urethritis.[44]

Prostatitis

In sexually active male adolescents dysuria, frequency, perineal or low back pain, and urethral discharge may be associated with prostatitis. Rectal examination may reveal an enlarged, tender prostate and some urethral discharge may be expressed. Staphylococci and enteric bacilli are often cultured, but it is likely the etiology is diverse and similar to the causes of urethritis.[38] Rarely, *Haemophilus influenzae* may be present.[62] Metronidazole and trimethoprim/sulfamethoxazole are most useful.[110]

Vaginitis

Clinical Manifestations

Most patients with vaginitis seek medical assistance because of dysuria,[31] discharge, irritation, foul smell, dyspareunia, and, rarely, associated systemic symptoms. However, many patients with vaginal inflammatory lesions may not have discharge or may be asymptomatic. Cervicitis is also present in many sexually active women with vaginitis.

Etiology

The commonest causes of vaginitis in infants and children are related to poor hygiene, and include fecal soiling, foreign bodies, trauma, bubble bath[136] and, occasionally, acquired enteric infections, such as shigellosis.[129] Chlamydiae, ureaplasmas, mycoplasmas and pinworms may also be present.[188]

TABLE 10–6. Etiology of Vaginitis

- In sexually active patients:
    - *Trichomonas vaginalis*
    - *Candida albicans*
    - Nonspecific: *Gardnerella vaginalis*
    - Mycoplasmas
    - Chlamydiae
- Infants/children who are not sexually active:
    - Foreign body with superinfection
    - Enteric bacilli
    - Streptococcus[58]
    - Shigella[129]

In sexually active women, vaginitis is most commonly due to Trichomonas, yeasts, or to Gardnerella[2] (Table 10–6), Trichomonas is estimated to be the most frequent cause of vaginitis in the United States,[52] where approximately 2½ million cases per year are seen.[113]

Diagnosis

Clues to the causes of vaginitis include the age and sexual activity of the patient, as mentioned above. The approach to history-taking, physical examination, and treatment needs to be modified accordingly.[39] In addition, characteristics of the vaginal discharge are important. Trichomonas, for example, is usually associated with a greenish, foul-smelling, and irritating discharge. Pruritus and burning sensations are common. In contrast, yeast infections are often associated with a creamy white discharge, sometimes with a curd-like component. These may be pruritic but are less irritating in most cases. Furthermore, the discharge of nonspecific vaginitis is generally nonirritating but often has a fishy odor.[13] The pH of this discharge is often above 4.5, and small coccobacilli are seen within epithelial cells (called "clue" cells).[177]

Specific diagnoses depend on careful smear and culture examinations of the vaginal discharge and lesions. The cervix and vulvar region should also be examined. If systemic signs are present, other examinations and cultures may be indicated. The fishy odor associated with the discharge of nonspecific vaginitis is accentuated in an alkaline pH or when the discharge is alkalinized with potassium hydroxide.

The Papanicolaou smear may disclose inclusion body-containing cells in approximately 25% of patients whose cultures are positive for Chlamydia.[34] Unfortunately, cultures are the only reliable method currently available for the accurate diagnosis of cervicitis and vaginitis due to Chlamydia or Mycoplasma.

Treatment

Treatment regimens for the major causes of vaginitis are outlined in Table 10–7. Despite the fact the nonspecific vaginitis is probably polymicrobial in etiology, metronidazole is commonly effective,[114] possibly because it reduces the anaerobic flora. If the patient is pregnant, administration of amoxicillin 500 mg q.i.d. for approximately 1 week is useful. Contacts should be treated if the condition is recurrent, since men may carry and transmit Gardnerella, as well as Candida and Trichomonas.

All adults colonized with Trichomonas, including sexual partners of infected patients, should be treated with a single 2-g dose of metronidazole.[74] If the woman is in the first trimester of pregnancy, local clotrimazole can be tried, but the success rate is much lower. Treatment of Trichomonas in a lactating woman should consist of a 2-g dose of metronidazole, with interruption of breastfeeding for a 24-h period after treatment is begun.

Recurrent or persistent vaginitis are frequently noted. Trichomonas and yeast cultures are the most sensitive means to make a diagnosis in such cases. Trichomonas cultures should be used for patients with negative wet-mount examinations, but who have persistent symptoms or recurrent infections. These cultures may also be used to diagnose Trichomonas resistant to metronidazole. Recurrent cases should be treated with higher and more prolonged doses of metronidazole, when possible. A careful search for colonized sexual contacts is also useful. Some newborns remain colonized, even symptomatic, after birth because of persistent urogenital infection. Respiratory colonization with Trichomonas in patients with pneumonia has also been reported.[122] Treatment consists of metronidazole 25 mg/kg/day by mouth for approximately 1 week. It

TABLE 10–7. Treatment of Vaginitis

- In individuals who are not sexually active:
  - Remove foreign body.
  - Institute proper hygienic measures.
  - Treat specific pathogen.
  - Suspect child abuse if sexually transmitted pathogen is causative.
- In individuals who are sexually active:
  - *Gardnerella vaginalis*
    - Metronidazole 500 mg PO b.i.d × 7 days
  - *Trichomonas vaginalis*
    - Metronidazole 2 g PO, single dose
  - Candida
    - Nystatin topically b.i.d × 5–7 days
    - or
    - Clotrimazole topically b.i.d × 5–7 days

is worthwhile to remember that several causative agents may coexist in patients with vaginitis and that more than one treatment may be required.

Candida vaginitis is treated with topical application of clotrimazole,[173] miconazole,[112] or nystatin. Sexual contact with infected individuals, use of oral contraceptives and antibiotics, and poor hygiene favor persistence and recurrence. In infants diaper dermatitis and diarrhea are also implicated. Persistent and extensive infection, in the absence of the above predisposing factors, suggests the possibility of gastrointestinal colonization,[124] but also may indicate underlying immune dysfunction, particularly when it is associated with weight loss and opportunistic infections with other microorganisms.

Pelvic Inflammatory Disease

Epidemiology/Pathogenesis

Pelvic inflammatory disease is an important manifestation of infection with *N. gonorrhoeae,* although many other microbes are also causative.[155] Both early and late complications are possible.[135] It is estimated that more than 850,000 cases occur in the United States each year.[66] In most instances, this is an infection acquired by microorganisms that reach the uterus, fallopian tubes, and ovaries by the ascending route from the vagina and cervical area. Occasionally, the presence of an intrauterine device increases this risk. Other predisposing factors include intercourse with many different partners, a prior history of pelvic inflammatory disease, and menstruation.[66] Infections associated with intrauterine devices are usually more localized to the area around the foreign body and endocervicitis is often associated with it. Barrier and oral contraceptives may offer some protection.[93]

Etiology

Pelvic inflammatory disease is usually of polymicrobial etiology.[202] Particular pathogens may be seen in certain settings, including *M. tuberculosis* in endemic populations, and *A. actinomyces* in patients with intrauterine devices[201] (Table 10–8). Gonorrheal or chlamydial infections are believed to be important in the pathogenesis of most cases, even if the organisms are not recovered from the pelvic site of infection.[155]

Rarely, pyosalpingitis may be due to uncommon vaginal flora, such as *Haemophilus influenzae.*[33]

Clinical Manifestations

Signs of pelvic inflammatory disease include lower abdominal pain and tenderness, adnexal tenderness, fever, and chills. Patients may vomit and

TABLE 10–8. Etiology of Pelvic Inflammatory Disease

- Anaerobic bacteria
  - Peptococcus
  - Bacteroides
  - Peptostreptococcus
  - *Actinomyces israelii*
- Aerobic bacteria
  - *N. gonorrhoeae*
  - Streptococcus, including group D
  - Staphylococcus
  - *E. coli*
  - Corynebacterium
  - *Mycobacterium tuberculosis*
- Mycoplasma
  - *M. hominis*
  - *Ureaplasma urealyticum*
- *Chlamydia trachomatis*
- Viral: herpes simplex

may also have acute peritonitis and pelvic abscesses. Many patients are thought to have ectopic pregnancies or appendicitis, and have laparotomies because of the severity of their signs and symptoms.

Diagnosis

The diagnosis is made clinically and by pelvic examination, which demonstrates tenderness of the uterine and adnexal organs.[155] Vaginal and/or cervical discharge and lesions may also be present. Cervical and vaginal cultures are indicated, as are cultures of any suspicious lesions. One should search for viruses as well, since herpes simplex may present with erosive endocervicitis and may contribute to the pathogenesis of pelvic inflammatory disease in some cases. Gram stain and culture of exudates from cervical or cul-de-sac lesions may also be useful. Although culdocentesis is helpful in obtaining specimens for culture, the invasive nature of this procedure and the expense of multiple cultures often relegates this test and multiple cultures to diagnosis of patients who do not respond to initial therapy or who have recurrent disease. Pregnant patients and those who have conditions characterized by pelvic masses or intense peritoneal signs should also be examined in this way. Rarely, laparoscopy may be used to verify the diagnosis and to obtain cultures. The type of culture should be guided by the clinical signs and history, as the diversity of etiologic agents is great (Table10–8).

Treatment

Most patients with pelvic inflammatory disease should be hospitalized; the exceptions are those whose illness is very mild. Appropriate antibiotic regimens for oral therapy of such nonhospitalized patients are difficult to design for two reasons. One is the polymicrobial nature of the infection, and the other is the relatively high failure rate associated with such antibiotic programs (about 15–20%). Hospitalization is required for all patients with severe illness, for pregnant women, for those who fail to respond to outpatient management, and for those in whom poor compliance and followup are anticipated. Patients with intrauterine devices and mass lesions should also be hospitalized for the removal of the foreign body and drainage.

Several antibiotic regimens are appropriate for the treatment of these patients (Table 10–9). As indicated above, specific cultures may be useful in guiding therapy in selected patients. Examination of sexual contacts is important, as many will have active gonorrheal, chlamydial, or ureaplasmal infections. The major responsibility for control of this condition in the community falls in the hands of public health officials, since education and case-finding are critical.

TABLE 10–9. Treatment of Acute Pelvic Inflammatory Disease

Hospitalized patients	
Doxycycline 100 mg IV b.i.d.	
plus	× 4 days or > 48 h after defervescence
Cefoxitin 2 g IV q.i.d.	
followed by: doxycycline 100 mg PO b.i.d. × 1 week	
If intrauterine device or abscess is present	
Remove foreign body and drain abscess	
plus	
Clindamycin 600 mg IV q.i.d.	
plus	× 4 days or > 48 h after defervescence
Gentamicin 2 mg/kg IV t.i.d.	
followed by: clindamycin 450 mg orally q.i.d. × 1 week	
Nonhospitalized patients (oral route)	
Chloramphenicol 75 mg/kg/day, divided q 6 h	
plus	
Doxycycline 100 mg b.i.d.	× 7–10 days
plus	
Trimethoprim-sulfamethoxazole 160 mg TMP/800 mg SMZ q 12 h	

Complications

Pelvic inflammatory disease should not be considered of minor consequence, since chronicity with hydrosalpinx and pelvic adhesions may result. The latter may cause severe and recurrent lower abdominal pain and even bowel obstruction.[135] Dyspareunia and tuboovarian abscesses may also result. More frequently, infertility and ectopic pregnancies are direct consequences of previous pelvic inflammatory disease.[19] The morbidity associated with these conditions is extensive.

Epididymitis/Orchitis

Etiology/Clinical Manifestations

Epididymitis usually presents as an acutely painful and swollen scrotal mass, more correctly called epididymoorchitis, since both epididymal and testicular inflammation are usually present.[150] This is extremely rare in young infants and children, in whom it is usually due to enteric bacilli and, occasionally, *Haemophilus influenzae,*[178] Pseudomonas,[36] or Salmonella.[192] Tuberculosis is a possible cause of epididymitis at all ages, and is often associated with renal infection.[42]

At one time mumps orchitis was common in sexually active men, but in communities when mumps immunization is widespread epididymoorchitis is almost always related to sexually transmitted infections, such as those due to gonococcus, Chlamydia,[77] and Ureaplasma. Rarely, *Neisseria meningitidis* may be causative.[198] When associated with urethritis, the condition usually appears in the second to third week of urethral discharge. Swelling is associated with fever, chills, redness, induration, and extreme tenderness.

Diagnosis

Since the etiology of epididymitis is diverse, cultures of the urethra, urine, epididymal aspirate, and blood should be obtained before treatment.[10] If skin lesions are present, they should also be cultured. The differential diagnosis of epididymitis should include torsion of the testis, mumps, various tumors, hernias, and posttraumatic conditions. If radionuclide scan or ultrasound indicates decreased blood flow, immediate surgical consultation is recommended.[150]

Therapy

Therapy in the infant age group should be directed against *E. coli* (e.g., gentamicin 7.5 mg/kg/day divided q 8 h IV). These patients require hospitalization and careful observation. If response to therapy is not seen quickly, surgical intervention is recommended, since the differential diagnosis includes conditions that urgently require surgical therapy or biopsy diagnosis.

In sexually active men, treatment is directed against the three common sexually transmitted infections such as those caused by *N. gonorrhoeae*, chlamydiae and ureaplasma. Hence, tetracycline 500 mg orally four times a day for 10 days is a useful regimen. Response to therapy within 24–48 h should be seen; if it is not, surgical conditions or other infectious etiologies should be considered. These may include tuberculosis or fungal infections. Bedrest, scrotal support, antipyretics, and analgesics are also important components of the treatment program.

Gonorrhea

Gonorrhea is most frequently seen in adolescents. Although nonvenereal transmission has been described,[56] the vast majority of cases are sexually transmitted. Child abuse should be ruled out in all cases of gonorrhea in prepubertal children; pharyngeal infection is particularly frequent in these patients.[69]

Gonorrhea is usually localized to the urethra in men, the vagina in prepubertal girls and cervix in sexually mature girls. The rectum[105] and other nongenitourinary sites can also be involved.

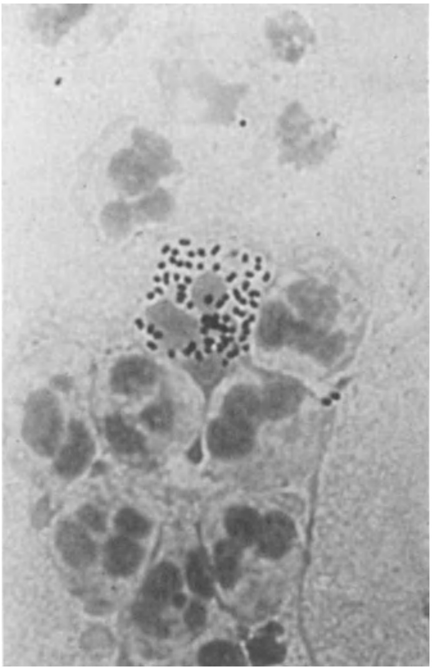
Clinical Manifestations

Gonorrhea is characterized by a 2–8-day incubation period after sexual intercourse, followed by a sudden onset of dysuria and urethral discharge in men, and leukorrhea in women. Symptoms are generally localized and do not include fever. The discharge is thick, profuse, and yellow, although considerable variability may be seen. Asymptomatic carriage of *Neisseria gonorrhoeae* can be seen in both men and women.

Systemic illness due to gonorrhea is unusual, but more frequent in young women than men. It usually consists of fever, arthritis, and skin lesions due to gonococcemia. The lesions begin as erythematous macules on the extremities, and progress to papules with areas of central necrosis.[17] Septic arthritis may also be present in approximately 1% of adolescent girls, but is quite unusual in men.[180] Rarely, focal infections, such as pyomyositis,[175] and even endocarditis,[182] are reported. Fulminant gonococcal sepsis has been documented in a 19-year-old after splenectomy for Hodgkin disease.[6]

Proctitis (often related to anal intercourse), pharyngitis (often related to fellatio),[181] conjunctivitis,[139] and other rare localized infections can also been seen.

Figure 10–2. Appearance of *N. gonorrhoeae* in urethral discharge as visualized by gram stain.



Diagnosis (see also Urethritis)

The demonstration of gram-negative intracellular diplococci in men (Fig. 10–2) and in prepubescent girls is useful; however, the vaginal flora in mature women is likely to contain other Neisseria species. Culture of the urethral or cervical discharge is confirmatory. Diagnosis of gonorrhea in prepubescent girls is most efficiently made by culture of vaginal swab specimens, even though there is very little discharge. Pharyngeal and rectal swabs should be included in the workup of sexual contacts in children with suspected gonorrhea, and if sexual practices suggest these are likely sites of involvement in sexually active patients. Pharyngeal cultures in all adolescents with suspected gonorrhea, have been recommended regardless of stated sexual practice.[20] Blood, joint fluid, and ocular cultures may be indicated in some patients as well.[27]

If there is a delay in inoculation and culture of the specimen, then appropriate transport methods should be used.[94] These utilize growth medium in a carbon dioxide environment which supports gonococcus at ambient temperatures. This organism is particularly susceptible to the effects of drying, cold, and overgrowth by other bacteria. Immunologic and other rapid diagnostic methods may be applicable for screening selected populations; however, bacterial culture remains the most reliable method.[50]

If the history and presenting features, as well as the characteristics of the exudate, do not suggest gonorrhea, then appropriate smears and cultures for other causes of sexually transmitted infections and acute urethral syndromes should be considered.

Treatment

Several drug regimens are useful (Table 10–10), depending on the site of infection and the susceptibility of the infecting strain of gonococcus.[191] Spectinomycin is effective in both children and adults with penicillin-resistant gonorrhea.[148] Cefotaxime 25 mg/kg (maximum 1 g) can also be given intramuscularly (without probenecid) for the treatment of gonorrhea resistant to both penicillin and spectinomycin.[5] Trimethoprim/sulfamethoxazole (80 mg/400 mg) should be given as a single daily oral dose for 5 days for pharyngitis due to penicillin-resistant strains. Erythromycin should be substituted for tetracycline in pregnant women and, given orally, has also been used successfully in some patients with disseminated infection.[180]

Whichever course of therapy is chosen, careful attention should be given to case-finding, compliance, and interruption of sexual intercourse for 3 or 4 days after treatment has begun or until the discharge stops, whichever is longer. If compliance is ensured, and reexposure to an infected contact does not occur, then penicillin-resistant gonococcus infection[84] and nongonococcal urethritis should be considered in patients with persistent or recurrent discharge. All patients with gonorrhea should have followup cultures 4–7 days after completion of treatment, as well as serologic tests for syphilis at the time of diagnosis and approximately 2 months later.

It should also be remembered that several causes of urethritis may coexist in the same patient. Public health reporting, surveillance, and hygienic and sexual counseling are important. Education of sexually active adolescents regarding preventive measures should concentrate on hygiene and use of condoms, and spermicides[85] which have some activity against *N. gonorrhoeae.*

Complications

Gonococcus may also cause prostatitis, epididymitis, and orchitis in men, and arthritis, ulcerative skin lesions, salpingitis, and pelvic inflammatory disease in women. Perihepatitis is occasionally noted as well.[109] Infertility and prematurity may also be associated with gonococcal and other causes of urethritis and genital infections in women. Late complications of gonococcal urethritis may also include urethral stricture and infertility in both sexes.

Vaccines are not yet available, but may be developed and used for prophylaxis in high-risk groups in the future.[183] For now, sex education,

TABLE 10–10. Antibiotic Treatment of Gonorrhea

	Pitfalls
Urethritis: One Dose	
Amoxicillin 50 mg/kg (maximum 3 g) orally + oral probenecid 25 mg/kg (maximum 1 g)	Inactive against Chlamydia and in anorectal or pharyngeal infection
or	
Procaine penicillin G 100,000 units/kg (maximum 4.8 million units) + probenecid (as above)	Pain at infection site; allergic reactions; inactive against Chlamydia
or	
Spectinomycin 40 mg/kg (maximum 2 g) IM	Ineffective for incubating syphilis and against Chlamydia
or	
Urethritis: multiple dose	
Tetracycline hydrochloride 50 mg/kg/day (maximum 2 g) in four divided doses × 7 days	Dependence on compliance; resistance to tetracycline; ineffective in anorectal infection
Penicillin-resistant *N. gonorrhoeae*	
Spectinomycin (as above)	As above
or	
Cefoxitin 50 mg/kg (maximum 2 g) IM plus probenecid (as above)	Inactive against Chlamydia
Pharyngeal gonorrhea	
Tetracycline (as above)	As above
or	
Procaine penicillin plus probenecid (as above)	As above
Anorectal gonorrhea	
Procaine penicillin plus probenecid (as above)	As above
or	
Spectinomycin (as above)	As above
Disseminated gonorrhea (arthritis, dermatitis, bacteremia)	
Aqueous crystalline penicillin G 100,000 units/kg/day (maximum 10 g) intravenously × 7 days	Inactive against Chlamydia
or	
Amoxicillin orally plus probenecid (as above) followed by amoxicillin 75 mg/kg/day in four divided doses × 7 days	Inactive against Chlamydia
or	
Cefoxitin 100 mg/kg/day (maximum 4 g), intravenously in four divided doses × 7 days (effective against penicillin-resistant gonorrhea)	Inactive against Chlamydia

postexposure antibiotic prophylaxis, use of condoms, early treatment, and epidemiologic surveillance are the major control measures.

Genital Herpes

Epidemiology/Etiology

Genital herpes infections are being recognized more frequently in the United States than ever before.[25] Herpes simplex type 2 virus is usually spread by direct contact with infected lesions, although colonized mucosa, with or without local symptoms,[121] and contaminated inanimate surfaces are potentially infectious.[104] Herpes simplex type 1 virus may also be transmitted sexually.[78]

Clinical Manifestations

Sexual transmission of herpes simplex virus is frequent. The location of the lesions depends on sexual practices. Hence, oral, anal, and rectal involvement may be seen in addition to the more classic penile, vulvar, vaginal, and cervical lesions.[78]

The initial genital lesions are often painful, and associated with localized lymphadenopathy, fever, and malaise. Itching and vaginal discharge are common in women, and urethral discharge may be seen in men.[25] The duration of the illness is between 2 and 4 weeks with considerable viral shedding and local spread.[71] Occasionally, viremia and extragenital foci of infection, including meningoencephalitis, cutaneous lesions, splenomegaly, and generalized lymphadenopathy may occur. Proctitis is suggested by anorectal pain, dysuria, sacral paraesthesias, and rectal ulcers.[64]

Some initial episodes are much less symptomatic. These are felt to represent primary expression of disease in patients with preexisting immunity against type 2 herpes simplex virus (the commonest cause of genital herpes infections) or against the related type 1 virus (Chapter 7). Recurrent disease is characterized by a shorter duration of lesion formation, fewer lesions, less viral spread, and fewer systemic symptoms. Most of these lesions clear within 8 days.[72]

Diagnosis

Vesicles in the genital region are most suspect. Giant cells can be seen in Tzanck or Papanicolaou smears of scrapings from these lesions in approximately one-half of cases.[25] Direct visualization of viral antigen in such specimens can be made in about 70% of patients by use of immunoperoxidase or immunofluorescent methods. Viral culture is most specific and usually provides results within 48 h. Seroconversion occurs with primary infection but there is usually no humoral antibody response in recurrent infection.

Treatment

The only effective method of prevention for this condition is avoidance of contact with infected lesions. Analgesics, antiinflammatory agents, sitz baths, and compassion are the mainstays of therapy. The primary disease can also be treated by topical application of 5% acyclovir ointment or with intravenous acyclovir 15 mg/kg/day, divided q 8 h, for 5 days.[26] Enough ointment should be applied approximately every 3 h (except during sleep) to cover all lesions for about 1 week. This will reduce shedding of viruses and decrease the duration of the illness; however, the latter effect is seen only in patients with primary infection.[146] Oral acyclovir may have the same effect on patients with recurrent disease;[132] however, recurrence is not prevented.[18] Chronic administration of oral acyclovir may be effective in decreasing the frequency of recurrences in selected patients.[174]

Because of the recurrent nature of the illness in many patients, and the cosmetic and pyschosocial morbidity, a variety of preventive and treatment measures have been attempted.[159,186] Many patients are desperate enough to try almost anything. A review of the various treatment modalities, however, cautions that there are none of proven efficacy, other than those mentioned above, and potential side effects are associated with many.[71]

The coexistence of herpes with other sexually transmitted infections should be kept in mind when considering diagnostic and therapeutic approaches. Child abuse should be suspected when genital herpes is diagnosed in pediatric patients who are not sexually active.

Prognosis

Although some initial episodes of genital herpes infections are prolonged and associated with severe pain and disability, most cases are self-limited and do not recur. Rare acute complications include penile necrosis and urethral stricture,[140] neurogenic bladder,[163] and endometritis.[154] The frequency of recurrences is extremely variable and sometimes related to stress, menstruation, sexual activity, and trauma.[72] Primary genital infection is most dangerous to the newborn if the mother has active infection around the time of delivery (Chapter 3).

Late complications include the association of genital herpes virus infection with the development of cervical carcinoma, believed to be a result of host cell genome transformation by viral DNA.[51] A direct cause and effect relationship, however, has not been proved, but the association is strong enough to recommend yearly Papanicolaou smear examinations in all women who had genital infection with herpes.

Chlamydial Genitourinary Infections

Clinical Features

The incubation period for chlamydial urethritis is usually between 1 and 3 weeks, although much longer intervals are noted, particularly in patients who are predominantly asymptomatic. Many of the features of chlamydial genitourinary infections are similar to those of gonorrhea. Thus, the patients are sexually active, and present with frequency, dysuria, urethritis, vaginal discharge, or, occasionally, gross hematuria.[164] As many as 50% can be asymptomatic.

The condition is seen more frequently in very sexually-active populations and in those with poor hygiene. The most characteristic presentation in men is persistent urethral discharge after treatment for gonorrhea. Proctitis has also been described in association with anal intercourse. Most frequently, women are either asymptomatic or have a clear scanty vaginal discharge, with or without acute urethral signs.[171] In approximately 20% of children examined, both gonorrhea and *Chlamydia trachomatis* infections coexist.[147]

Diagnosis

A smear of the exudate visualized by Wright or gram stain in patients with signs of urethritis will usually contain polymorphonuclear leukocytes. Pyuria may also be present. Both urethral and cervical cultures should be obtained in patients and in contacts.[134] Serology can be used to confirm the presence of this infection, but is seldom a practical approach for diagnosis or case-finding.

Treatment

The mainstay of treatment for *Chlamydia trachomatis* infections is tetracyclines; however, erythromycin or sulfonamides may also be used (Table 10–11).

In general, the available diagnostic techniques (cultures and serology) are underutilized, and treatment for Chlamydia with tetracycline[179] is based on presumptive criteria. In many cases 7 days of treatment may be adequate;[16] however, patients who have a recurrence after only 1 week's therapy should be treated for 14 days.[179] Contacts should also be examined and treated, as they may be a source of reinfection. Remember, asymptomatic proctitis or cervicitis may be present in sexual contacts of these patients. Since pelvic inflammatory infection (and subsequent infertility) may follow asymptomatic chlamydial cervicitis, treatment is recommended even for asymptomatic colonized patients.[49] *Chlamydia trachomatis* pharyngitis or genitourinary infections in prepubescent subjects should also suggest sexual abuse.

TABLE 10-11. Treatment of Chlamydial Infections (Adult Doses)[a]

Cervicitis/urethritis/vaginitis	[Both index case and contact(s)]
Tetracycline hydrochloride 500 mg orally *or* Erythromycin 500 mg orally	divided four times/day × 7 days
Cervicitis/urethritis/vaginitis in pregnancy	
Erythromycin (as above) *plus* Tetracycline hydrochloride (as above) for contacts	

[a] See Chapter 2 for Pediatric Doses

Complications

Many other organs may also be involved in Chlamydia infections. Manifestations include pneumonia, meningoencephalitis,[63] epididymitis, prostatitis, pelvic inflammatory disease, perihepatitis,[22] Reiter syndrome, and urethral stricture.[44] The disease may also manifest as endometritis,[30] infantile pneumonia (Chapter 3), and conjunctivitis (Chapter 4). Moreover, it is becoming obvious that *Chlamydia trachomatis* is a cause of prematurity and infertility.[126] Hence, microbiologic diagnosis of chlamydial infection should prompt specific therapy. The only limitation is the expense and complexity of the diagnostic techniques. Future improvements in laboratory diagnosis may facilitate programs of diagnosis and management with far-reaching results.

Lymphogranuloma Venereum

Etiology/Diagnosis In the tropics, specific serotypes (L1, L2, and L3) of *Chlamydia trachomatis* are associated with a single or several small inoculation lesions, which are usually painless, rapidly healing papulovesicles.[153] The secondary stage of this infection consists of malaise, fever, myalgia, and greatly enlarged inguinal and femoral lymph nodes. Skin breakdown and sinus formation may follow. A tertiary stage consisting of rectovaginal fistulas, rectal strictures, and proctitis is also described. Diagnosis depends on culture of the Chlamydia or seroconversion measured by the more commonly employed complement-fixation test; titers of 1:64 or greater are diagnostic.

The treatment of this condition consists of tetracycline 500 mg, by mouth, four times a day for at least 3 weeks.[115] Alternative programs include doxycycline 100 mg/day orally for the same period of time. Erythromycin 500 mg four times a day can also be used. If fluctuant, lymph nodes should be aspirated, although incision and drainage should not be carried out, since healing time is prolonged and the disease process may be lengthened. Late complications of lymphogranuloma venereum include stricture and fistula formation. These occasionally require surgical intervention.

Syphilis

The incidence of syphilis has been increasing in the last 2 decades. The effects of primary disease are most frequently seen in late adolescence, in the second decade, and in the newborn period. Congenital syphilis is discussed in Chapter 3. Other treponemal infections are discussed in Chapter 7.

Clinical Manifestations

Primary syphilis is usually seen within 10–90 days of exposure and is manifest as a single chancre (Fig. 10–3) or ulcer in the genitourinary tract, oral cavity, or anal margin, depending on sexual practice and site of inoculation.[59] This is usually beefy red, nontender, and firm, with a clean surface and raised border. There are no systemic signs; however, adjacent lymph nodes are often enlarged but not tender.

Approximately 2–10 weeks after the primary lesion, the patient may develop fever, generalized lymphadenopathy, malaise, headache, and a rash involving the palms and the soles. Some patients, however, may have nodular papular lesions resembling cutaneous lymphoma, but sparing the palms and soles.[9] Mucous membrane lesions and condylomata lata may also be present in the perianal and perivaginal regions. Syphilitic hepatitis[92] is a rare but serious complication of this systemic stage.

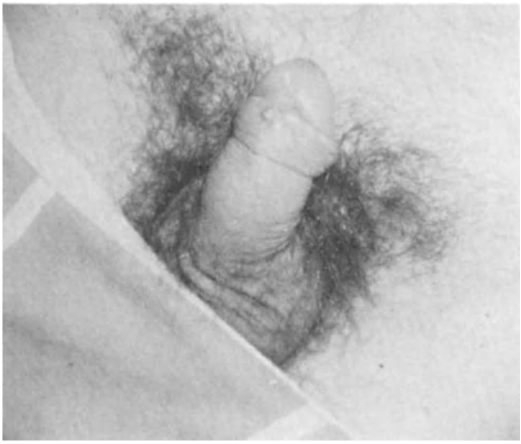


Figure 10–3. Primary chancre of syphilis.

The latent (asymptomatic) stage of syphilis begins after the secondary stage, although several recurrences characteristic of secondary disease may occur. Tertiary disease, which appears anywhere from 3 to 10 years after the last secondary recurrence, may take the form of neurosyphilis, including meningoencephalitis, paralytic disease, optic atrophy, or central nervous system gumma. Late tertiary disease most often involves the cardiovascular system, in particular, the aortic valve and pulmonary artery.

Diagnosis

Syphilis is most rapidly diagnosed by dark-field examination of material from the primary chancre or secondary skin or mucous membrane lesions. These specimens should be handled with care, as they are highly infectious. Serologic tests for syphilis are mandatory in all cases.[65]

The VDRL or RPR tests can be used for screening. These are flocculation tests comprising antigens that react with antibody against nontreponemal reagin and show positive results within 2–6 weeks after infection. If tests are done at an early stage and produce negative results they should be repeated after a 6-week interval. When these screening tests are positive, the more specific FTA-abs test should be used to confirm the diagnosis. This test detects antibody against treponemal antigen, although it does not differentiate between the various species of treponema.

Biologic false-positive results are seen with nontreponemal antigen tests in patients with pneumonia, other acute infections, and after immunization. These can be seen in cerebrospinal fluid as well as in serum.[118] These generally have low titers and the FTA-abs test is nonreactive. Although most of these results are transient, drug addiction, chronic hepatitis, leprosy, and collagen-vascular diseases may cause chronic false-positive reactions, particularly with the screening tests. Biologic false-positive FTA-abs tests are less common, but are seen in patients with diabetes mellitus and lupus erythematosus. The *Treponema pallidum* immobilization test may be useful in these patients.

Treatment

The treatment of syphilis is outlined in Table 10–12. The cerebrospinal fluid should be examined to rule out the presence of neurosyphilis, except in the primary stage of disease. Aggressive therapy is warranted considering the grave consequences of untreated syphilis. Followup serology is recommended at 3, 6, and 12 months after treatment. The VDRL or other nontreponemal antigen screening test titers will usually fall within 12–24 months, although the FTA-abs test often remains positive for life.[46]

TABLE 10–12. Treatment of Syphilis

Primary or secondary syphilis
  Benzathine penicillin G 2.4 million units IM at one session
  If patient is allergic to penicillin
    Tetracycline 500 mg PO q.i.d. × 15 days
  If patient is allergic to penicillin and pregnant
    Erythromycin 500 mg PO q.i.d. × 15 days (treat newborn with penicillin)
Latent syphilis (more than 1 year duration)
  Benzathine penicillin G 2.4 million units IM, once/week × 3 weeks
  If patient is allergic to penicillin
    Tetracycline 500 mg PO q.i.d. × 30 days
Neurosyphilis
  Aqueous crystalline penicillin 24 million units IV/day, divided q 4 h, × 10 days, followed by benzathine penicillin G 2.4 million units IM, once/week × 3 weeks
  If patient is allergic to penicillin
    May require desensitization and treatment.

Chancroid

Chancroid is an ulcerative, sexually transmitted infection prevalent in many countries including Korea, Brazil, Mexico, and the Philippines. Although chancroid is occasionally seen as an endemic disease in North America, most cases in this country are imported.[98] One or several, pain-

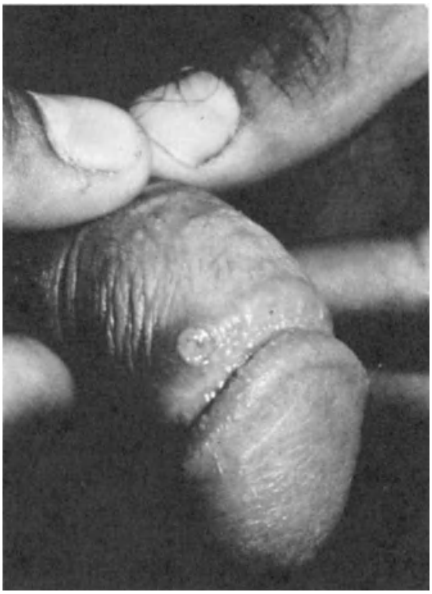


Figure 10–4. Chancroid ulcer. (Courtesy of Dr. P. Rettig.)

ful, nonindurated genital ulcers (Fig. 10–4) develop 3–5 days after inoculation and, in about 50% of cases, are associated with inguinal lymphadenopathy, which may become fluctuant. There are usually no systemic signs. Diagnosis is made by culture of the causative organism *Haemophilus ducreyi,* from the ulcer and/or from the infected lymph nodes. Selective media must be used for culture of these bacteria.[37]

Treatment

Antimicrobial treatment consists of erythromycin 500 mg, four times daily, for a period of 10 days, or 160 mg trimethoprim/ 800 mg sulfamethoxazole, given twice daily for the same period of time.[48] Amoxicillin plus clavulanic acid can also be used.[43] Treatment should be prolonged if there is delay in clearing the ulcers or slow improvement in the lymphadenopathy. Aspiration of fluctuant lymph nodes, as well as soaks and debridement of ulcers, will also hasten recovery. Contacts should be treated in a similar fashion. Other causes of genital ulcers, some of which may coexist with chancroid, should also be ruled out.

Sexually Transmitted Diseases in Abused Pediatric Patients

Special consideration of children who have been abused, or adolescents who have been raped, is worthwhile. These cases require microbiologic and serologic followup, and psychosocial intervention.[97] The multiple etiologies of sexually transmitted diseases need to be considered,[10] and the patient treated if any of these is identified in the assailant[14] (Table 10–13). Gonorrhea, syphilis, Trichomonas, or condyloma acuminata were detected in 13% of 403 children suspected of being sexually abused; two infections were present in each of five patients.[197] Occasionally, evaluation may also be indicated for infections due to herpes simplex, Gardnerella, ectoparasites, or enteric pathogens.

TABLE 10–13. Recommendations for Victims of Child Abuse[14]

Culture (sites depend on history) for *N. gonorrhoeae,* Ureaplasma, Chlamydia, Trichomonas
Syphilis serology
Treatment of specific infection
Pregnancy test in postmenarchal females (may need to be repeated at followup)
Followup cultures as necessary, and serology for syphilis at 6 weeks

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11

Cardiovascular Infections

Endocarditis

Infections of the cardiovascular system are infrequent in normal children. The majority of patients with endocarditis have underlying structural heart disease; however, it is estimated that 5% of cases of endocarditis in children, and up to 50% of cases in newborns and young infants occur in the absence of preexisting cardiac anomalies.[45] Incidences of mortality and morbidity continue to be high, despite the availability of potent antimicrobials because of the difficulty in diagnosis and the severity of the hemodynamic effects. Improved survival of children with structural cardiac abnormalities, through advances in cardiac surgery and use of prosthetic devices, provides increased opportunities for infectious complications.

Pathogenesis

Congenital anomalies of the heart presenting the highest risk of endocarditis are those associated with a high velocity of blood flow. These are seen in patients with endocardial cushion defects, tetralogy of Fallot, bicuspid aortic valve, ventricular septal defect with aortic insufficiency, and less commonly, with isolated ventricular septal defects, patent ductus arteriosus, and aortic or pulmonary stenosis.[45] Adequately repaired ventricular septal defects and uncomplicated atrial septal defects present little risk. Patients with rheumatic heart disease, and those who have had valvular repairs, with or without prosthetic implantations, are also at high risk, as are individuals with mitral valve prolapse.[9]

Conditions or procedures associated with bacteremia present a risk of endocarditis to these patients. These include periodontitis, skin infections, urinary tract infections, pneumonia, sinusitis, and osteomyelitis.

Bacteremia is commonly reported after dental and urologic procedures, but can also occur after endotracheal intubation, cardiac catheterization, tonsillectomy, ventriculoatrial shunt insertion, bronchoscopy, and other surgical procedures. Squeezing a pimple, dental flossing, vigorous brushing of teeth, water massage of gums in the presence of periodontitis present a risk as well.[45] In some situations, such as drug addiction, the individual inadvertently creates the bacteremia directly by injecting contaminated material intravenously. The presence of central venous catheters and other intravascular foreign bodies may also be important in the pathogenesis of endocarditis (Fig. 11-1). Removal of these is often critical to effective therapy because of normalization of flow and eradication of the focus of infection.

Etiology (Table 11–1)

Staphylococcus aureus and *Streptococcus viridans* are the most common causes of endocarditis in infants and children.[28] Staphylococcus is particularly important in the newborn and young infant, even in those without underlying structural cardiac abnormalities.[47] *S. viridans* colonization is most common after respiratory infections or dental procedures, whereas group D Streptococcus infections and gram-negative endocarditis may be seen

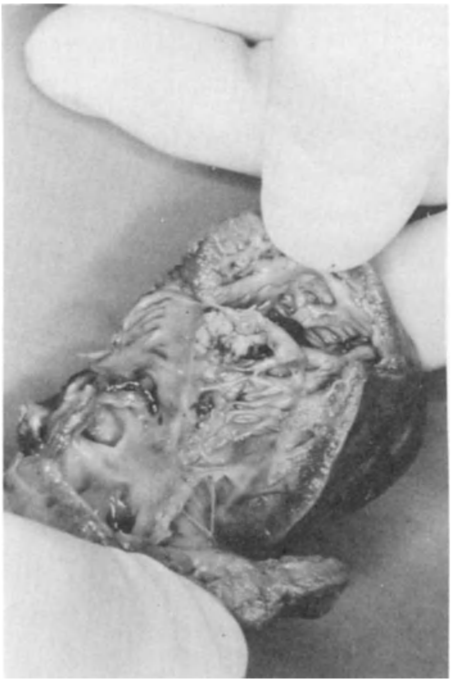

Figure 11–1. Vegetation on tricuspid valve. (Courtesy of Dr. G. Altshuler.)

TABLE 11-1. Microbial Etiology of Endocarditis

- Bacteria
  - Staphylococcus
  - *Streptococcus viridans*
  - Streptococcus, group D
    - Enterococcus (*S. faecalis, S. faecium, S. durans*)
    - Nonenterococcus (*S. bovis, S. equinus*)
  - *Streptococcus pneumoniae*[26]
  - *Streptococcus pyogenes*[70]
  - Streptococci: nutritionally variant[41]
  - Pseudomonas[55]
  - Pasteurella[31]
  - Brucella
  - Kingella[54]
  - *Listeria monocytogenes*[59]
  - Bacteroides
  - Serratia[25]
  - Haemophilus[50]
  - Cardiobacterium[19]
  - *Streptobacillus moniliformis*
  - Actinobacillus[34]
  - Diphtheroids[40]
  - Wall-defective bacteria (L forms)[44]
  - Mycobacteria[42]
- Fungi
  - Candida
  - *Candida (Torulopsis) glabrata*[24]
  - Aspergillus
  - Penicillium
- Rickettsia
  - *Coxiella burnetii*[49]
- Chlamydiae
  - *C. psittaci*[29]
  - *C. trachomatis*
- Viruses
  - Coxsackie[7]

after urologic procedures, including surgery and catheterization. Cardiac prostheses may be colonized by *S. aureus* or *S. epidermidis,* as well as *Candida albicans* and, occasionally, other yeasts or fungi and bacteria. These opportunists most often present within the first 3 months after cardiac surgery.[28] Infections of prosthetic valves after this time are more commonly due to *S. viridans.* As characteristics of the host change and more complicated surgery and catheterization procedures are used, other rare infectious etiologies are being noted. Hence, rare gram-negative bacteria,[61] diphtheroids, unusual streptococci, and even rickettsiae are reported. Drug addicts, who inject drugs intravenously, are also prone to opportunistic endocarditis, such as that due to *Pseudomonas maltophilia.*[78] Although the older literature suggests that 10–15% of infective endocarditis has no defined etiology, this is usually due to partial treatment and the difficulty of identifying unusual etiologic agents with specific nutritional requirements, as well as rickettsiae, and possibly other causes of infections. Since management varies considerably with different etiologies, it behooves us to expend extra diagnostic efforts in patients with "bacteriologically negative endocarditis."

Clinical Manifestations

Endocarditis may present in several different fashions, depending on the age of the patient, the underlying heart disease and/or abnormality, and the etiologic agent. The most serious forms of infection are of acute onset and often do not have many of the features of classic subacute bacterial endocarditis. Rather, these patients manifest high fever, obtundation, chills, and severe malaise. A new or changed cardiac murmur may be present and acute embolic phenomena may also be seen. Since such emboli may involve the central nervous system in approximately 20% of cases, the child may occasionally present with a syndrome suggestive of brain abscess, meningitis, or focal encephalitis. When this occurs in a child with a preexisting heart condition, endocarditis should be considered. Emboli may also involve lungs, spleen, and kidneys, where the effects can mask the cardiac manifestations. Occasionally, patients will have hypotension or acute congestive heart failure as part of their presentation.[66] Patients with severe infection of a prosthetic valve or septal graft may also present with acute hemodynamic changes, such as severe valvular insufficiency or left to right shunting. Much more rarely, patients may present with myocarditis or dysrhythmias because of involvement of myocardial conduction systems. Many of these cases of acute onset are due to *Staphylococcus aureus*; however, the onset may be less abrupt and difficult to diagnose in newborns.[69]

A more insidious onset is characteristic of endocarditis due to *S. viridans* or *S. epidermidis.* These children have fever, anorexia, weight loss, and other nonspecific signs and symptoms. These are the patients most likely to manifest retinal and cutaneous petechiae and hemorrhages, splenomegaly, anemia, arthritis or arthralgias, aseptic meningitis, or glomerulonephritis. New or changing murmurs and/or congestive heart failure may also be seen.

Persistent bacteremia may be the only objective sign of endocarditis in newborns and young infants. The diagnosis is suggested when bacteremia recurs or is associated with the development of a murmur, anemia, and, possibly, splenomegaly. As in older patients, hematuria and cardiovascular signs (new or changing murmurs, dysrhythmias, hypotension, congestive heart failure) or embolization often suggest the diagnosis.[47]

Diagnosis

The old adage that states fever in a patient with underlying heart disease is due to endocarditis until proven otherwise, is still useful. Cardiac patients are special and should not be treated empirically with antimicrobial therapy without consideration of endocarditis. That is not to say that streptococcal pharyngitis or otitis media should not be treated appropriately, but that in patients with urinary tract infection, pneumonia, and other potentially bacteremic conditions, at least one blood culture should be done prior to antibiotic therapy. If a diagnostic procedure is performed (such as percutaneous bladder aspiration, thoracentesis, lumbar puncture), then a second blood culture following the procedure is also useful. Special historical clues to endocarditis include exposure to sheep (because of the possibility of Q fever endocarditis) and other unusual exposures to infections (e.g., cryptococcosis, histoplasmosis, coccidioidomycosis, intravenous drug abuse, etc.).

In addition to the clinical features mentioned, these patients have specific laboratory findings, especially bacteremia. Those who present within 3 months of cardiac surgery, or with an acute toxic clinical picture, should probably have a buffy coat smear examination for bacteria in and among the white blood cells. These patients should also have a minimum of two 5 ml blood cultures, since approximately 80% of cases of endocarditis will be positive after the first blood culture and 90% after the second blood culture. It may not be possible to obtain additional cultures in newborns and infants, but more cultures are generally not required in disease of acute onset. In those with a slower onset and mild illness several blood cultures can be spaced over a 6–24-h period. It is rarely necessary to obtain more than four, and almost never more than six, blood cultures in these patients.

When Staphylococcus or diphtheroids are suspected, it is worthwhile to perform a skin culture after preparation of the blood culture site. Examples include patients who have had recent cardiac surgery, individuals with intracardiac prosthetic devices and vascular grafts, and drug addicts, as well as patients with skin infections. Skin culture may provide a clue to the adequacy of skin preparation before obtaining blood cultures, and often aids the interpretation of sparse and inconsistent bacterial growth. A high serum titer of teichoic acid antibodies may be present in these patients with staphylococcal infection.[67]

Although anaerobic causes of endocarditis are rare, it is useful to culture some of the blood anaerobically, if enough material is available.[17] Specific serology for *Coxiella burnetii*[52] and viruses may be indicated in selected cases, as may be fungal and mycoplasma cultures and serology.

Cultures of any other affected sites, and a urine culture, should also be obtained in all cases. Thus, skin infections, periodontitis, dental abscesses, urogenital lesions, etc., should be appropriately examined and cultured as well. Antibiotics should be removed from the blood obtained for cultures by appropriate resins, or neutralized by specific enzymes. As in the case of many complicated infections, the extra effort taken to obtain blood cultures and to communicate with the microbiology laboratory will provide useful information in many cases.

Examination for group B streptococcal antigen in serum and urine is indicated in newborns, and pneumococcal and Haemophilus antigens in older patients. Virus cultures of respiratory and gastrointestinal sites are indicated in patients with suspected myocarditis. Although the endocardium is usually not involved, some patients with myocarditis may present with congestive heart failure and dysrhythmias, which in the presence of underlying cardiac disease or anomalies may be difficult to differentiate from endocarditis.

Nonmicrobiologic laboratory aids to diagnosis are also useful. Echocardiography can be used to demonstrate vegetations and myocardial abscesses.[33] These should be periodically performed in patients with high-risk cardiac lesions and probable episodes of bacteremia, and in all cases of endocarditis early in the course[63] to assess vegetation size and valvular function. Similarly, a baseline electrocardiogram is useful to study the function of the conduction system.

Many of these patients are anemic, and have leukocytosis and increased erythrocyte sedimentation rates. The erythrocyte sedimentation rate is useful in order to follow the progress of the infection and may aid therapeutic decisions. Similarly, sequential quantitation of immune complexes may be helpful.[6] Hypocomplementemia and hyperbilirubinemia may be manifestations of immune complex formation and hemolysis, respectively. Urinalyses and measurements of renal function are useful to document the degree of renal involvement.

Acute Complications

When a diagnosis of endocarditis is suspected, the patient should be hospitalized for purposes of investigation and management. In addition to administration of antibiotics, careful surveillance for development of congestive heart failure, dysrhythmias, and embolic phenomena are required. The status of these patients can change dramatically. These approaches should be modified in light of host characteristics. For example, a patient who has developed acute endocarditis within a few weeks of cardiac surgery may have an extremely fulminant course with rupture of valves, chordae tendinae, or septal perforation. Those with prostheses in place may have displacement of the foreign body and sudden hemodynamic changes. Approximately 20% of pediatric patients may have embolic complications.[16] Signs of embolization will depend on the site of infarction and the characteristics of the vegetation. If they are infected at the time of embolization, mycotic aneurysms and focal abscesses may develop. Emboli frequently involve the lungs, brain, extremities, spleen, kidneys, mesenteric vessels, and, rarely, coronary arteries with resultant infarction.[16]

Treatment (Table 11–2)

Initial antibiotic therapy should be directed at the most likely causes of endocarditis. Bactericidal antibiotics are preferred. In cases with an acute fulminant onset, therapy should be started immediately after obtaining appropriate cultures. In such instances, intravenous oxacillin and gentamicin are useful for the therapy of *S. aureus, S. viridans,* and some group D Streptococcus species. Many gram-negative bacteria will also be treated with this regimen. Infection that manifests less acutely is usually not due to *S. aureus* and initial therapy may include penicillin, particularly if respiratory or dental foci are suggested by the history and clinical features. If genitourinary and/or gastrointestinal foci are implicated, gentamicin should be added to penicillin.

Antibiotic therapy is initially administered intravenously because of the need to present rapid, high serum concentrations to endocardial vegetations. The mechanism of drug transport to the microbes within vegetations is by passive diffusion and, therefore, creation of a large gradient is useful. Adequate serum concentrations are usually ensured by maintaining a peak serum bactericidal activity of at least 1:8, or an antibiotic concentration in the serum that is at least eight times the minimum inhibitory concentration, or four times the minimum bactericidal concentration for the infecting organism. *S. viridans* can be treated with penicillin alone if the bacteria are sensitive to < 0.05 μg/ml of penicillin.[74] Remember that recent exposure to penicillin may select *S. viridans* relatively resistant to penicillin.[36] In a small percentage of patients, the rate

TABLE 11–2. Treatment of Common Causes of Endocarditis

Streptococcus viridans
  Penicillin G 200,000 units/kg/day IV, divided q 4 h × 4–6 weeks
  Add gentamicin 7.5 mg/kg/day for first 1–2 weeks.
Staphylococcus
  Oxacillin 200 mg/kg/day IV, divided q 4 h × 6–8 weeks
  Add gentamicin 7.5 mg/kg/day for first 1–2 weeks.
  Add rifampin 15 mg/kg/day *or* vancomycin 40 mg/kg/day, if tolerant or methicillin-resistant strain (both rifampin and vancomycin may be required in selected cases).
Enterococcus
  Penicillin G 200,000 units/kg/day IV, divided q 4 h, *or* ampicillin 200 mg/kg/day, divided q 4 h, IV, *plus* gentamicin 7.5 mg/kg/day divided q 6 h × 6 weeks

of bacterial killing (usually for streptococci) may be enhanced by the addition of an aminoglycoside, a practice I prefer for the first 2 weeks of therapy. Serum concentrations and toxicity must be monitored. Continue the aminoglycoside intravenously for that period, except in patients with exquisitively sensitive bacteria and with rapid defervescence and bacteriologic eradication. Defervescence is defined as a drop in the fever (which usually occurs within 1 week after the initiation of antibiotic therapy), a rise in the serum complement, a fall in the erythrocyte sedimentation rate, and a decrease in the amount of circulating immune complexes.[6] Absence of congestive heart failure and embolic phenomena, and stabilization of the cardiovascular status are also useful clinical markers of improvement. Blood cultures should be obtained at the expected trough of serum antibiotic concentrations, and should be repeated daily until three 5 ml volume negative cultures have been collected. All of these features should be considered together in making decisions about duration of therapy.[75] Generally, therapy is continued for a minimum of 4 weeks; however, *S. aureus* and fungal infections in patients with previous cardiac surgery and prostheses should be treated for a minimum of 6 weeks. The oral route can be used early in some patients with highly sensitive bacteria susceptible to well-absorbed antimicrobials.[51]

Patients with staphylococcal endocarditis should be treated with either oxacillin 200 mg/kg/day given intravenously every 4 h, or penicillin if the *Staphylococcus* strain is sensitive. Vancomycin 40 mg/kg/day is recommended for patients who are allergic to penicillin. Tolerant staphylococci (as indicated by a wide disparity between the inhibitory and bactericidal concentrations) can present specific treatment problems, suggested by persistent bacteremia and clinical signs despite conventional antistaphylococcal therapy. The addition of rifampin,[3] or rifampin plus vancomycin, may be useful in such cases.[2]

Enterococci are usually resistant to penicillin ($\geq$ 1 μg/ml) and should be treated with a combination of penicillin G, 300,000 units/kg/day or ampicillin 200 mg/kg/day intravenously every 4 h, plus gentamicin 7.5 mg/kg/day, intravenously every 6 h.[73]

Patients allergic to penicillin should receive vancomycin 40 mg/kg/day. The doses given are estimated and should be modified with respect to the susceptibility of the organisms and the pharmacokinetics in each patient. The potential for disease due to strains highly resistant to aminoglycosides should also be recognized.[38]

Surgical therapy may be required in patients with prosthetic valves or infected patches who do not respond in a satisfactory manner.[12] Congestive heart failure, dehiscence of the valve, persistent bacteremia (beyond 1 week) despite appropriate antibiotic therapy, major embolization, and the presence of dysrhythmias and/or myocardial abscesses may be other indications for surgery.[10] Because these events may occur suddenly, patients at high risk for these complications should be followed by both the surgeon and the pediatrician. A team approach is recommended for the care of these patients, in consideration of the complexity of microbiologic diagnosis, antibiotic therapy, and surgical/medical management.

Three days after cessation of therapy, and at any time clinical signs suggest recurrence, blood cultures should be repeated. Followup hemodynamic and echocardiographic studies are useful in ascertaining the degree of valvular involvement and as a baseline in the event of a recurrence.

Prevention

Antibiotic prophylaxis is recommended for high-risk patients in order to prevent colonization and infection during periods of bacteremia. Although this is commonly considered for dental, surgical, and urogenital procedures, it should also be kept in mind for any procedure or disease commonly associated with bacteremia. The source of the bacteremia is important as well. If the site infected is the upper respiratory or oropharyngeal area, then *S. viridans* is the most likely invader. If it is genitourinary, enterococci may be more common. These principles are different for hospitalized patients, in whom opportunistic infections are frequent and gram-negative bacteria may commonly reside in the upper respiratory tract. Patients with skin lesions, those on hemodialysis, and those with ventricular-peritoneal shunts are at increased risk of bacteremia due to *S. aureus* and/or *S. epidermidis.* Although the American Heart Association, and others, have outlined specific prophylactic regimens, some individualization seems warranted. For example, patients with rheumatic heart disease who have been receiving penicillin prophylaxis for prolonged periods may have *S. viridans* relatively resistant to penicillin in their oropharyngeal flora.[23]

Erythromycin or ampicillin may be more appropriate prophylaxis for these children. The need for excellent oral hygiene in such patients cannot be overemphasized. Recent observations suggest that penicillin-resistant *S. viridans* may be more frequent than suspected, even in children without penicillin exposure for 2 months prior to bacteremia associated with dental procedures.[23] If these studies are confirmed, alternative prophylactic regimens will be required. In any event failures of prophylaxis against infection with sensitive bacteria have been also reported.[13] With these principles and reservations in mind, the reader is referred to the drugs and doses for prophylaxis outlined in Table 11–3.

Prognosis

Factors that affect the outcome of endocarditis are extremely variable. The youngest patients, and those with major cardiac abnormalities, have the poorest outcome, as do patients with prosthetic valves and fungal

TABLE 11-3. Antibiotic Prophylaxis for Patients at Increased Risk for Endocarditis

For dental procedures (use parenteral route if patient is unable to take drug orally or if surgery imminent).

- Phenoxymethyl penicillin PO 100 mg/kg/day. Begin 2 h before surgery and divide q 6 h thereafter × six doses.
- If the patient is allergic to penicillin: Erythromycin 20 mg/kg PO 2 h before surgery, then 10 mg/kg PO q 6 h × six doses.
- If the patient has a prosthetic valve (or preliminary to cardiac surgery) or he has skin furunculosis: Add dicloxacillin 100 mg/kg/day to above (vancomycin 40 mg/kg/day for patients allergic to penicillin).

For genitourinary and gastrointestinal procedures (usually parenteral route required)

- Add gentamicin 7.5 mg/kg/day IV for six doses (divided q 6 h) *and* substitute IV penicillin G 100,000 units/kg/day for phenoxymethyl penicillin.

endocarditis. The time of diagnosis, the appropriateness of therapy, the use of early surgical treatment, and the general condition of the host are also important. In a recent review of endocarditis in the pediatric population, 19/50 patients died, with most of the deaths due to *Staphylococcus aureus* in patients under 10 years of age.[28] On the other hand, occasional cures, even after the occurrence of myocardial infarction, suggest that the ability to develop collateral vessels is great in young infants with endocarditis.[16]

It is possible that the use of M-mode and sector scan echocardiograms may improve our ability to diagnose endocarditis early, a critical factor in appropriate management and survival.[27] Prophylaxis for patients who have recovered from endocarditis and, therefore, have injured valves or endocardial surfaces, may also be required to prevent subsequent infection.[20] Endocarditis is rare in the pediatric age group, and the diagnosis in its earliest stages is most difficult, yet critical for a favorable outcome.

Fungal Endocarditis

Fungal infections of the heart are being seen with increasing frequency, particularly in relation to cardiac surgery, use of prosthetic valves, and in immunodeficient patients and transplant recipients. *Candida sp.* are most frequently seen, although a variety of opportunistic fungi have been described.[58] Among these *Mucor* is most likely to invade blood vessels, the myocardium, and the pericardium.[68] Predisposing factors, in addition to surgery and the presence of foreign bodies, include umbilical venous catheterization in newborns, intravenous hyperalimentation, use of corticosteroids and antibiotics, and malnutrition. Features of fungal endocarditis are similar to those of endocarditis due to other causes; however, right-sided disease after surgery of intravenous catheterization may be extremely difficult to diagnose clinically and by blood culture. Repeated pulmonary embolization and pulmonary hypertension may be clues to endocarditis in some patients.[30] Embolic phenomena and consumptive coagulopathy suggest the possibility of Aspergillus infection in children after open heart surgery.[5]

Treatment of fungal endocarditis usually requires amphotericin B, either alone or combined with 5-fluorocytosine. In vitro susceptibility studies of the infecting fungus will help guide therapeutic programs. In addition, repeated blood cultures, echocardiograms, and titration of Candida antigens in the serum and urine of these patients may provide useful guidelines. 5-Fluorocytosine, ketoconazole, or miconazole should not be relied upon as the sole therapeutic agent, except in rare circumstances. Although medical therapy may be successful, prolonged treatment is usually necessary and surgical valve replacement may be the only hope of permanent cure in some of these patients.[53] Since medical cures have been seen, however, it would seem useful, in the hemodynamically stable individual, to attempt a program of medical therapy first.

Myocarditis

Epidemiology

Infections of heart muscle are probably more frequent than is realized because of the mild and nonspecific nature of the associated signs and the benign prognosis in the vast majority of cases.[15] Some estimates suggest that transient abnormalities of the heart can be noted in as many as 5% of subjects experiencing a respiratory viral infection.[71]

Estimates as high as this usually are based on studies of enzymes or electrocardiograms performed during community outbreaks of coxsackie B virus infections. Both the pericardium and the myocardium are often inflamed, especially in cases of viral infections.

Newborns seem particularly susceptible to severe illness when infected with coxsackie B virus, and myopericarditis should be included in the differential diagnosis of sudden infant death.

Pathogenesis

Little is known about the exact pathogenic mechanisms involved in the development of myopericarditis, although direct tissue injury by virus invasion and inflammatory responses of the host undoubtedly participate in the acute phase (Fig. 11–2). Persistent virus infection (in the infective or latent form) and immunopathologic injury have been suggested as responsible for the more severe and chronic cases.

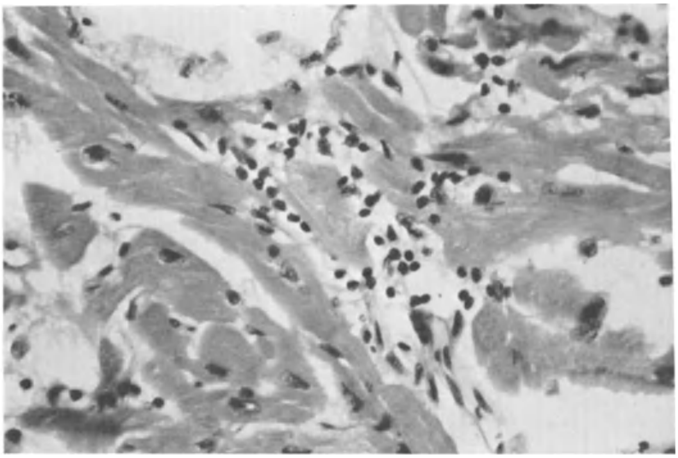

Figure 11–2. Gross and microscopic appearance of acute myocarditis. (Courtesy of Dr. G. Altshuler.)

Etiology

In North America, coxsackie B viruses account for most of the recognized cases of myocarditis, although in other parts of the world diphtheritic, tuberculous, or parasitic causes may still be present (Table 11–4). The possibility of tuberculosis should be considered early, as should chlamydial,[56] mycoplasmal,[18] and rickettsial causes, since treatment is available. Careful history taking will usually rule out other rare, but treatable, causes of myocarditis, such as diphtheria, fungal infection, and syphilis. Recent experience suggests that one should look for *Chlamydia trachomatis* in patients presenting with respiratory infection and myocardial disease.[57] Patients with infectious mononucleosis, influenza, arbovirus,[14] and cytomegalovirus syndromes[77] should also be watched for this complication.

Clinical Manifestations

The vast majority of patients with myocarditis have little in the way of specific symptoms to suggest involvement of the heart.[21] Acute respiratory infection is the commonest prodromal event, although occasionally patients with infectious mononucleosis, influenza, and Rocky Mountain spotted fever may present with more systemic signs. Thus, cough, lethargy, poor appetite, hepatomegaly, and fever may be seen. More specific signs include chest pain, shortness of breath, persistent tachycardia, gallop rhythm, pericardial friction rub, and muffling of the heart sounds. The latter two signs are more specific for pericarditis, whereas some of the former signs and arrhythmias are more frequently seen with myocarditis. In rare instances, endocardial involvement may result in myocardial infarction or sudden death. The latter may also be due to valvular dehiscence.

TABLE 11–4. Infectious Causes of Myocarditis

- Viruses
  - Coxsackie (especially B-4)
  - ECHO
  - Mumps
  - Adeno
  - Varicella
  - Epstein-Barr
  - Influenza
  - Cytomegalovirus
  - Arbovirus
  - Polio
- Chlamydiae
  - *Chlamydia trachomatis*
  - *Chlamydia psittaci*
- *Mycoplasma pneumoniae*
- Rickettsiae
  - Rocky Mountain spotted fever (*R. rickettsii*)
  - Typhus
  - Q fever
- *Helminths*
  - Trichinella
  - Echinococcus
  - Schistosoma
  - Toxocara
- Bacteria
  - Diphtheria (*C. diphtheriae*)
  - Tuberculosis (*M. tuberculosis*)
  - Syphilis (*T. pallidum*)
- Fungi and yeasts
  - Actinomyces
  - Blastomyces
  - Candida
  - Aspergillus
  - Histoplasmosis
  - Coccidiomycosis
  - Sporotrichosis
  - Cryptococcosis
  - Cysticercosis
- Protozoa
  - Trypanosoma (American Chagas disease)
  - Toxoplasma
  - Leishmania

Diagnosis

In addition to the clinical signs, the chest radiogram may reveal an increase in heart size and, later, myocardial calcification. Patients with chest pain, dysrhythmia, and dyspnea usually have electrocardiographic changes demonstrating the rhythm abnormalities (occasionally including complete heart block),[18] or elevation of the ST segment, or T wave inversion or flattening. Throat culture for group A *Streptococcus pyogenes* and serologic tests of streptococcal antibodies should be included in the evaluation of these patients, since it is important to rule out rheumatic fever. Elevated serum concentrations of creatine phosphokinase, or SGOT, reflect cardiac muscle injury. Patients with significant pericardial effusions, and occasionally those with heart block or severe congestive heart failure, may require operative procedures that include pericardiotomy, drainage, and, occasionally, endomyocardial biopsy. Isolation of viruses should be attempted in each of these cases. Fluorescent antibody techniques for demonstration of viral antigen, and cultures to include other relevant causative agents outlined in Table 11–4, should be included, as directed by historical and physical findings.

In the rest of the patients, the specific etiologic diagnosis may be confirmed serologically. Therefore, serum and throat and rectal swabs should be obtained as early in the acute phase of illness as is possible, and a serum specimen during convalescence 2–3 weeks later. If meningoencephalitis is present (e.g., with coxsackievirus infection) cerebrospinal fluid should also be cultured. Seroconversion in cases of enteroviral infections can be confirmed by the development of a fourfold or greater rise in neutralizing antibody against the patient's viral isolate or epidemic strain. Rarely, fungi or opportunistic bacteria may invade the myocardium with severe complications.

Treatment

If the cause is known, specific therapy should be instituted early. For diphtheria, this includes administration of penicillin and specific antiserum. For other bacteria, Chlamydia, Mycoplasma, and fungi, specific antimicrobial agents should be prescribed. Epstein-Barr virus myocarditis should be treated with systemic acyclovir therapy for periods of 7–10 days.

In addition, patients will often require digitalis, diuretics (such as furosemide), bedrest, and careful observation for the development of arrhythmias and myocardial infarction. Specific chemotherapy for dysrhythmias, and even pacemakers, may occasionally be required. This description of treatment is directed at the obviously ill patient; however, the infection is self-limited and benign in the majority of community-acquired cases of myocarditis. Occasionally, echocardiography, computerized tomography, or ultrasonography may reveal thrombi in the heart or vessels, or emboli, suggesting the need for anticoagulation. Progressive myopericarditis may require surgical drainage of a pericardial effusion. Consideration of passive immunization with specific antibody may be given when the exact etiology is described, or with intravenous immunoglobulin in other cases, although there is no documented evidence that this will be helpful. This is somewhat different from the questions of therapy with adrenal corticosteroids because experimental evidence indicates a deleterious effect of steroids on coxsackievirus-induced myocarditis[35a].

Complications

Although most cases are benign, acute heart failure, serious arrhythmias, and myocardial infarction with sudden death have been described.[21] Congestive heart failure may be difficult to manage in the acute stages as well. It is uncertain whether long-term complications include valvular disease, an association suggested by the findings at autopsy of coxsackievirus antigen in endocardial and myocardial tissues of adult patients.

Prognosis

It is estimated that up to 5% of patients with acute coxsackie B virus infections have myocardial involvement.[71] Of these, as many as 20% may be symptomatic, 1–2% of whom may die. In the final analysis, this is not a common cause of death, but serious morbidity may result from acute heart block, myocardial infarction, and acute congestive heart failure. Whether myocardial scars persist and whether these contribute to cardiac disease in later years is speculative.

When the exact cause of myocarditis is unknown, coxsackie B virus (especially serotype 4) should be considered causative. In such an instance, no specific therapy is required and the prognosis is good in the majority of cases. Neonates may be an exception, as morbidity and mortality are pronounced in the first month of life. Although myocardial calcification may occur in these extremely ill patients, clearing of the calcification and complete recovery have been noted.[4]

Pericarditis

Epidemiology/Pathogenesis

Pericarditis is a rare, but life-threatening, condition. It is often associated with myocarditis, particularly when viral infection is responsible. In other cases, pericarditis is part of a generalized infection. This is illustrated in children with *Haemophilus influenzae* meningitis and pericardial involvement.[8] Sometimes, pericarditis is noted during the convalescent stage of an acute bacterial infection, so-called "postinfectious" pericarditis. This has been reported during convalescence of meningococcal infection in particular.[46]

The pericardial space normally contains 10–15 ml of fluid in children and young adults, but can accumulate as much as 1000 ml during acute inflammatory states. The hemodynamic changes associated with this fluid collection may prevent adequate cardiac output and lead to serious consequences. In the chronic stages, loss of pericardial elasticity due to calcification may bring about similar, although less rapid, changes.

Etiology

The most frequent causes of pericarditis are undoubtedly viral, with coxsackieviruses most prevalent.[11] Many of these inflammatory reactions go unnoticed in their acute stage, which sometimes accounts for the idiopathic nature of late developing constrictive pericarditis. The most dramatic presentation of pericarditis, however, is the acute suppurative form, which is most commonly due to *Staphylococcus aureus* and can be associated with a mortality rate as high as 50%, if untreated. Effective treatment requires early diagnostic pericardiocentesis, followed by surgical drainage and appropriate antibiotic therapy. The infectious causes of pericarditis are extremely diverse (Table 11-5); however, relatively few cases of each type have been described in detail. Noninfectious causes, including autoimmune and familial syndromes, with and without arthritis, should also be considered.[37]

Unusual causes of pericarditis include *Mycoplasma hominis* infection, reported in a newborn,[39] and varicella pericarditis, which has been noted with or without the presence of a chickenpox or a herpes zoster-like rash.[76] Amebic pericarditis can be seen after erosion of an amebic liver abscess into the pericardial space, although this is reported in fewer than 2% of patients with hepatic amebiasis.[22]

Clinical Manifestations

In patients old enough to report it, precordial pain is prominent and is usually associated with fever and malaise. The pain is greatest when the individual is lying down and may be referred to the left shoulder or arm.

TABLE 11-5. Infectious Causes of Pericarditis

- Acute suppurative pericarditis
  - *Staphylococcus aureus*
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Neisseria meningitidis*
- Postinfectious
  - *S. aureus*
  - *N. meningitidis*
- Tuberculosis
- *Mycoplasma hominis*
- *Mycoplasma pneumoniae*
- Fungi
  - Histoplasmosis[72] (*H. capsulatum*)
- Viruses
  - Coxsackie
  - ECHO
  - Influenza
  - Adeno
  - Epstein-Barr
  - Polio
  - Varicella
- Parasites
  - *E. histolytica*

It is often relieved by sitting up and may be associated with cough, weak pulse, tachycardia, and nausea. Although a friction rub is a characteristic physical finding, it is often absent early in the course of pericarditis. Other signs, such as decreased heart sounds, increase in neck vein distension, cardiac tamponade, and congestive heart failure with associated hepatosplenomegaly depend on the accumulation of large amounts of fluid in the pericardial space. Exaggeration of the normal drop in systolic blood pressure with inspiration to > 20 mm Hg (pulsus paradoxicus) usually indicates the presence of a large amount of fluid in the pericardial space as well. This sign can also be seen in severe asthma and emphysema, and in patients receiving positive-pressure ventilation.[20] Ascites and massive edema are late signs of congestive heart failure seen in both acute suppurative and constrictive pericarditis.

Diagnosis

The diagnosis of pericarditis is often elusive, particularly when it is due to one of the rarer causes (e.g., *S. pneumoniae, E. histolytica* or as part of bacteremic Haemophilus or meningococcal infections). The electrocardiogram, chest X-ray, and echocardiography are useful in confirming the diagnosis. Echocardiography will demonstrate a widening of the space between the pericardium and the myocardium, as well as identify myocardial dysfunction, which is often associated with the presence of pericarditis.[64] The heart is enlarged on chest radiogram and may take on a configuration often described as "water bottle" which is due to the large amount of fluid surrounding the base of the heart when the patient is in the upright position. This same fluid leads to the electrocardiographic changes of decreased voltage, and the clinical signs of muffled heart sounds, hepatomegaly, and distension of neck veins. Other electrocardiographic findings include elevated ST segments, T wave flattening and inversions, and tachycardia. If myocarditis is associated, other conduction abnormalities may also be noted.

The etiologic diagnosis of pericarditis is often dependent on the results of pericardiocentesis. When pericardial effusion is suspected, and the patient is symptomatic, this procedure should be carried out as soon as possible, and before the institution of antibiotic therapy. The fluid in acute suppurative pericarditis will contain many polymorphonuclear leukocytes, and the gram stain will usually reveal gram-positive cocci. In viral pericarditis a predominance of mononuclear cells may be present and the virus may be cultured from this material. Throat and rectal cultures for viruses should be obtained. Tuberculous fluid is usually straw-colored and contains a predominance of lymphocytes, although neutrophils may be present in the early stage. Mycobacteria may be cultured from the fluid or the pericardium. When pericardial tissue becomes available at surgery, finding typical granulomas, which are usually culture-positive, in the pericardium will establish the diagnosis of tuberculosis.[62]

Appropriate cultures and a search for antigens in the patient's pericardial fluid, serum, and urine should be carried out. Remember that *H. influenzae, S. pneumoniae,* and *N. meningitidis* antigens can be detected in all three sites in systemic infection. Serologic confirmation of the viral cause of pericarditis may be very important, should other studies not reveal the etiology and the patient have a prolonged or recurrent course. The treatment of tuberculous pericarditis is vastly different from that of infections due to common bacteria and viruses.

The differential diagnosis of pericarditis is broad and can be complicated (Table 11-6). For example, the difficulty of differentiating uremic and viral pericarditis was pronounced in a recently reported series of patients with renal failure.[48]

Treatment

Treatment of pericarditis depends on the stage of illness and the exact cause. Acute purulent pericarditis is usually attended by serious toxicity and may also be associated with congestive heart failure, cardiac tamponade, and/or systemic signs of infection. This represents a true medical emergency and immediate pericardiocentesis for diagnosis and relief of cardiac tamponade is indicated. This is usually done through a paraxyphoid anterior approach. In other cases, diagnostic pericardiocentesis can be done on a more elective basis. Definitive treatment of bacterial pericarditis requires a more aggressive surgical approach, usually drainage through a pleuro-pericardial window. Patients with constrictive pericarditis are also markedly improved after removal of as much of the calcified or fibrous pericardium as possible. The results of such therapy can often be dramatic, as exemplified by the return of a patient with protein-losing enteropathy and acquired immune deficiency to normal status after such surgery.[43]

TABLE 11-6. Noninfectious Causes and Differential Diagnosis of Pericarditis

Rheumatic fever
Rheumatoid arthritis
Lupus erythematosus
Uremia
Neoplasm (e.g., teratoma, Hodgkin disease, lymphosarcoma, leukemia)
Radiation
Thallasemia
Trauma
Pericardial cyst
Postpericardiotomy syndrome
Postmyocardial infarction
Myxedema
Benign recurrent pericarditis[1]

In addition to aggressive surgical approaches, antibiotic therapy is recommended for infections due to bacteria and mycobacteria. Generally, antibiotics of the penicillin and cephalosporin class reach concentrations in the pericardial space that equal serum levels within 2–4 h after systemic administration.[65] This is also true for aminoglycosides, therefore obviating the need for local antibiotic instillation at the time of surgery.[60]

Therapy for tuberculosis should include three drugs (isoniazid, rifampin, and ethambutol) and a fourth, pyrazinamide, if isoniazid-resistant bacteria are suspected. The use of corticosteroids in such cases is controversial, although they are often employed in the hope of delaying the development of fibrosis or calcification (in such cases, prednisone 2 mg/kg/day is added to the drug regimen for the first 2 weeks; thereafter, the dose is decreased by 2.5–5 mg/day at 2–3-week intervals over a period of 3 months).

Repeated pericardiocenteses are probably not an optimal treatment for recurrent pericardial effusions, whatever the cause. In fact, an aortic aneurysm has been reported in a 10-year-old girl with pericarditis due to *S. aureus* after several such procedures.[35]

Prognosis

The outcome in advanced purulent pericarditis may be poor. Death is usually due to the hemodynamic changes, particularly cardiac tamponade and acute congestive heart failure. Thus, early diagnosis will lead to the best prognosis. Once adequate drainage and appropriate chemotherapy are initiated, the outcome is good. Some patients will develop constrictive pericarditis and require further surgery.[32] Others, more rarely, may develop recurrent episodes of pericardial effusion. When this happens, the differential diagnosis should include autoimmune diseases as well. Adrenal corticosteroid therapy may markedly improve the symptoms of patients with some of these conditions and of those with recurrent idiopathic pericarditis.[20] In the final analysis, pericarditis is problematic because it is relatively rare and often difficult to diagnose. The etiologic spectrum is wide and includes both infectious and noninfectious causes. Because of this, aggressive diagnostic approaches are warranted. The results of appropriate and early treatment are most often successful.

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12

Systemic Infections in Normal and Immunocompromised Hosts

Generalized infectious diseases have been discussed in reference to the predominantly involved organ, e.g., endocarditis, meningitis, and pneumonia. Other infections manifest predominantly as fever without a specific source, or may present with only fever and lymphadenopathy (e.g., toxoplasmosis),[210] hepatosplenomegaly (Chapter 6), or fulminant sepsis. Lymphadenopathy is an important clue to the cause of persistent fever. Biopsy should be considered in patients with supraclavicular adenopathy, weight loss, prolonged fever, or in those with lymph nodes adherent to the overlying skin.[169]

Systemic Infections Presenting as Fever

Fever

Fever is a sign, not an illness, and needs to be considered as a clue to the presence of inflammatory conditions, including infectious diseases. The molecular basis of fever production, associated with endogenous pyrogen released from mononuclear phagocytes, and its effect on the thermoregulatory center of the hypothalamus, are reviewed elsewhere.[64] There are several other exogenous and endogenous sources of pyrogen, such as endotoxins, pyrogenic substances in blood products, and substances in the environment, that may contribute to disturbances in temperature regulation. Moreover, thermoregulatory center immaturity is particularly important in newborns, and dysfunction in patients with central nervous system pathology. Fever affects not only the well-being of the host, but several host defense mechanisms as well, including enhancement of leukocyte mobility, lymphocyte transformation, and interferon production.[168] Some of these effects are benign and may augment the patient's immune competence, as well as antibiotic and serum bactericidal activities.[197]

Temperature elevations need to be determined carefully. Hence, caution is urged in using chemical indicators applied to the surface of the skin (e.g. paper strip thermometers) to quantitate temperature elevations.[272] Although the fever pattern is seldom useful,[230] the duration and height of fever, and the age of the patient, may help diagnostic evaluation. In infants under 3 months of age, for example, temperatures of 40°C or greater are likely due to a serious infection.[215] Temperatures below 40°C may often be due to self-limited infections or to noninfectious causes.[320]

The treatment of fever includes use of light clothing, exposure to normal room temperature, and adequate hydration. Sponging small portions of the body with tepid water may also help. Salicylates and acetaminophen are effective antipyretics. Although their use in combination has been suggested, this carries a risk of enhanced toxicities of both drugs.[68] Response to these treatments should not detract from the accurate diagnosis of cause. Aspirin should be avoided during influenza outbreaks and in patients with varicella, in view of the possible association of this drug and these diseases with the development of Reye syndrome.

Acute Fever

Fever is one of the commonest manifestations of infection in individuals of all ages; however, infected newborns may not have a febrile response and hypothermia may be seen with brain injury, and in severe septic states with shock. The infant with fever requires special consideration because of the difficulty of localizing signs and symptoms in the first 2 years of life, the fulminant nature of many infections at this age, and the marked predisposition of infants to pneumococcal and Haemophilus infections. After the age of 2 years, the patient is more often able to help the clinician by describing specific symptoms and the clinical course of many illnesses is characteristic.

Upper respiratory infections, systemic viral syndromes, gastroenteritis, and otitis media are among the most frequent causes of acute fever in infants (Table 12–1). Septicemia, meningitis and pneumonitis are not uncommon and represent the most serious causes. Epidemiologic history is the key to the diagnosis of epidemic febrile illnesses, such as yellow fever, Marburg disease, Lassa fever and dengue[203] as well as other arenavirus hemorrhagic fevers, malaria, or schistosomiasis, Hepatitis with jaundice may suggest yellow fever in South America and Africa, but many hemorrhagic fevers may produce similar findings. Fever, erythematous rash on extremities, and arthralgia have occurred after ingestion of milk contaminated with *Streptobacillus moniliformis,* also called Haverhill fever.[295] Another rare cause of acute fever is hyperpyrexia, induced by anesthetics (malignant hyperthermia).[165]

TABLE 12-1. Causes of Fever in Infants Under 2 Years of Age[215]

More common	Otitis media
	Viral/nonspecific
	Viral/with rash or enanthem
	Viral/respiratory
	Viral/meningitis
	Pneumonia
	Gastroenteritis
	Bacteremia
Less common	Bacterial meningitis
	Urinary tract infection[275]
	Bacterial infection with rash
	Noninfectious conditions: e.g., malignancy, collagen-vascular disease
	Rickettsial infections:
	Rocky Mountain spotted fever
	Boutonneuse fever[225]
	Toxoplasmosis[305]

In the first 3 months of life bacteremia is often due to group B Streptococcus, and thereafter, to *Haemophilus influenzae* and *Streptococcus pneumoniae.* It is important to examine infants carefully for these systemic infections, even if otitis media is thought to be present. When there are no localizing features, the fulminant nature of some of these infections in infants should be remembered. The clinician may not have the luxury of watching the evolution of the illness in this age group, particularly in children with high fevers, irritability, and no localizing signs. Meningitis, bacteremia, and other systemic infections can proceed extremely rapidly and the onset of shock, seizures, and purpura are late events with a poor prognosis. How then can we approach these patients in a safe fashion?

These young infants should be examined under the most optimal conditions. The physician's judgment of the degree of illness is one of the most critical factors in determining the likelihood of bacteremia and focal septic infections.[332] The infant under 2 years who is inconsolable despite appropriate diminution of his fever and attempts to create a quiet but interesting environment is the one to worry about. Moreover, infants under 3 months of life who have fever with no identifiable source, or fever with presumed otitis media, should have a complete workup for sepsis, including blood culture, lumbar puncture, chest radiogram, and urine culture. A white blood cell count, urinalysis, and an erythrocyte sedimentation rate are also helpful. In fact, a white blood cell count of greater than 15,000 cells/mm^3 and an erythrocyte sedimentation rate of greater than 30 mm/h are important indicators of bacteremia in infants in the first 2 years of life.[51] Whatever the course taken, a careful followup at 24–48 h is an important component of the management of these patients, as localization and specific diagnoses may be evident in up to 20% of cases.

Persistent Fever/Fever of Unknown Origin (FUO)

Common infectious diseases are responsible for persistent fevers as well. When fever (defined as temperatures of 38.5°C or greater) lasts for longer than 2 weeks and ordinary examinations have failed to identify a cause, several other considerations are warranted. When there are no localizing clinical signs, these conditions have been variably grouped as "Fever of Unknown Origin." In analyzing 100 children satisfying this definition, the etiology was infectious in 52, collagen-vascular disease in 20, malignancies in 6, and miscellaneous or idiopathic conditions in 22.[259] Children under the age of 6 were more likely to have infections, whereas those above this age were more likely to have collagen-vascular diseases (Table 12–2).

Patients with prolonged fevers often have anorexia, fatigue, weight loss, chills, sweats, and abdominal pains, but no specific localizing findings. Sometimes the source is hidden, as in the case of peritonsillar abscess or intraabdominal lymph node hyperplasia.[189] A clue to the diagnosis in some of these cases may be provided by the presence of anemia and hypergammaglobulinemia, as reported in benign giant lymph node hyperplasia involving mesenteric lymph nodes.[220]

The diagnosis and management of children with persistent fevers is complicated, but clues may be provided by a detailed history, more than by any other specific test. Thus, suspicion of malaria, yersiniosis, an enteric fever, and tuberculosis might be forthcoming from epidemiologic information, including travel history, exposure to animals,[102] or illness in contacts. Similarly, weight loss, visual abnormalities, gastrointestinal signs, and psychosocial history may provide other clues. In the latter instance, recurrent fevers due to closely spaced benign infections, or factitious fever, should be kept in mind.[167] In appropriate countries relapsing fever should be considered.

Patients with persistent fever who have normal hematologic examinations, urinalysis, chest X-ray, and sedimentation rates are less likely to have serious infections, neoplasms, or autoimmune conditions. As many as 15% of patients with idiopathic persistent fever spontaneously improve within several months to years after identification of the syndrome. Physicians should keep this in mind when considering extensive hospitalizations and testing. Nonetheless, advances in radionuclide scans and computerized tomography have helped reduce the morbidity of investigation in these cases and have facilitated definitions of the etiology, particularly when focal intraabdominal abscesses are responsible. The latter may be particularly difficult to diagnose in infants who have sus-

TABLE 12-2. Causes of Fever of Unknown Origin

Infections	Infectious mononucleosis
	Urinary tract infection
	Tuberculosis
	Meningoencephalitis
	Pneumonia
	Bacteremia[32]
	Sinusitis
	Malaria
	Peritonsillar abscess
	Osteomyelitis
	Enteric/typhoid fever
	Endocarditis
	Hepatitis/hepatic abscess[157]
	Pelvic/intraabdominal abscess
	Louse-borne relapsing fever due to *Borrelia recurrentis*[183]
Drug-induced	Antibiotics
	α-Methyldopa
Neoplasms	Lymphoma
	Leukemia
	Sarcoma
	Leiomyoma
	Retinoblastoma[116]
Collagen-vascular	Juvenile rheumatoid arthritis
	Systemic lupus erythematosus
	Regional enteritis/ulcerative colitis
	Behçet syndrome
Metabolic/endocrine[72]	Malignant hyperthermia[165]
	Hyperthyroidism
	Phaeochromocytoma
	Riley-Day syndrome (familial dysautonomia)
Idiopathic	"Pseudo fever"[167]
	Benign giant lymph node hyperplasia[220]
	Ectodermal dysplasia
	Mucocutaneous lymph node syndrome
	Letterer-Siwe (histiocytosis)
	Familial erythrophagocytic lymphohistiocytosis[7]

tained a perforation of an inflamed appendix and in patients receiving corticosteroids.

Relapsing Fever

Relapsing fever is caused by *Borrelia recurrentis* infection and occurs predominantly in Africa, the Middle East, and Europe. This spirochetal disease is transmitted by lice and can be diagnosed by visualization of the bacteria in Wright-stained smears of the peripheral blood. Patients are usually febrile, toxic, and have splenomegaly. Treatment consists of administration of tetracycline, erythromycin, or chloramphenicol, but is occasionally accompanied by a Jarisch-Herxheimer reaction. Recent experience suggests that meptazinol, 300–500 mg intravenously, markedly diminishes this adverse reaction.[315]

Fever and Myalgia

Fever and myalgia are common components of several systemic infections (Table 12–3). Occasionally, myalgia is the most outstanding feature, and true muscle tenderness, and even swelling, are appreciated. This can be a component of trichinosis or influenza,[80] but may, more rarely, be due to bacterial myositis (called pyomyositis when muscle abscesses develop), caused by Streptococcus or *Staphylococcus aureus.*[126] This is more prevalent in the tropics than in the United States. Unusual causes, such as noncholera vibrios, may also be responsible.[164]

In some cases, myalgia is secondary to rhabdomyolysis, in which there is significant destruction of muscle and myoglobinuria. This has been described in infections due to influenza, coxsackieviruses, ECHO viruses,[155] herpes simplex, Epstein-Barr virus, and adenoviruses.[218] Occasionally, simultaneous infections with viruses or bacteria may cause acute muscular injury.[261] These are usually benign and self-limited conditions; however, fatalities caused by disseminated viremia and myositis due to echoviruses have been reported.[111]

In other situations, myalgia—a subjective phenomenon—is difficult to pinpoint etiologically, or even as a manifestation of an infectious disease. An example is so-called benign myalgic encephalomyelitis, in which groups of patients have transient myalgia and nonspecific systemic com-

TABLE 12–3. Systemic Infection With Fever and Myalgia

Trichinosis
Influenza
Coxsackievirus infections
Echovirus infection
Leptospirosis
Malaria
Babesiosis
Infectious mononucleosis
Adenovirus infection
Streptococcal/staphylococcal rhabdomyolysis or myositis
Combined infection (e.g., Streptococcus and Picornavirus)[261]

plaints, sometimes associated with low grade fever.[213] Psychologic factors are thought to be important in some of these outbreaks.

Myalgia, myositis, and rhabdomyolysis are, therefore, manifestations referable to systemic infections that may be quite common, as in the case of influenza, or quite unusual, as in the case of bacterial myositis. In some cases, when myalgia is associated with eosinophilia and periorbital edema, specific diagnoses (e.g., trichinosis) are suggested.

Typhoid and Enteric Fever

Epidemiology/Pathogenesis

Salmonella bacteremia and focal and systemic infections are seen after gastrointestinal colonization with various species of this genus. *Salmonella typhi* is the most virulent and causes a syndrome called typhoid fever, whereas other Salmonella species commonly cause enteric fever. Some prefer the latter term for all febrile patients with Salmonella bacteremia. Gastroenteritis is the predominant manifestation of Salmonella infections in industrialized countries; enteric and typhoid fevers are still prevalent in the third world countries.[36]

Man is the major reservoir for *S. typhi*; other Salmonella species are found in a wide variety of animals. Water and food contamination is important in the pathogenesis of this condition,[233] as are other predisposing factors, including malnutrition, intestinal schistosomiasis, and malignancies. Although excretion of Salmonella in the stools of infants under the age of 3 months may persist for 12–15 weeks, prolonged carrier states are uncommon in childhood. However, adults, particularly women over the age of 50, are most likely to remain persistent stool excretors of *Salmonella typhi* after acute infection or asymptomatic colonization.[181]

Clinical Manifestations

After a variable incubation period that averages 1 week after ingestion of contaminated water or food, an abrupt onset of fever, anorexia, abdominal pain, hepatosplenomegaly, lethargy, apathy, and upper respiratory symptoms are noted.[319] Rash, in the form of rose spots, as well as anemia, constipation and sore throat are frequently present. Sore throat may be due to tonsillitis, a rare complication of typhoid fever.[151] Neurologic symptoms, especially lethargy, are common. Rare neurologic presentations include psychosis and hearing loss.[58]

Mortality in typhoid fever has been reduced considerably by appropriate antibiotic therapy and management of shock. Still, approximately 4% of patients die and 10–15% have relapses after treatment. The cause of death is usually due to toxemia and septic shock, due to gram-negative organisms or gastrointestinal bleeding or perforation.

Diagnosis

The diagnosis of these systemic febrile infections is confirmed by culturing Salmonella from the blood. The bacteremic phase lasts from 1 to 2 weeks and may be associated with only fever and lethargy in many patients. Appropriate epidemiologic history, anemia, and splenomegaly are other clues. Although bradycardia and leukopenia are often described in typhoid fever, children may have more than 25,000 white blood cells/mm^3.[38] Rarely, patients present with hemolysis, splenic abscess (or other focal abscesses), or pleural effusion.[89]

After the first week of illness, bacteria are shed in the stool and may also be found in the urine. Thus, blood, stool, and urine cultures are indicated in patients in whom a diagnosis of typhoid or enteric fever is suspected.

Indirect means of making the diagnosis rely mainly on the use of Salmonella agglutinin titers against H or O antigens. These tests are relatively nonspecific, however, as several Salmonella serotypes that cause uncomplicated gastroenteritis may elevate these titers for long periods of time. Nevertheless, in endemic populations, a fourfold rise in titer of these antibodies is usually indicative of typhoid or enteric fever.[292] The *Vi* antibody can be used for seroepidemiologic definition of asymptomatic carriers in the community.[181]

Treatment

In the acute phase, Salmonella bacteremia may cause death due to hypovolemic septic shock. A period of high risk also occurs after the initiation of antibiotic therapy, presumably due to the release of endotoxin from injured or killed bacteria. Patients with severe toxicity may benefit from the use of dexamethasone 3 mg/kg, followed by 1 mg/kg q 6 h for 2 days.[131] Most patients, however, remain relatively stable during therapy.

Antibiotic susceptibility patterns vary from region to region, but resistance to chloramphenicol, trimethoprim-sulfamethoxazole, and ampicillin have been reported with increasing frequency.[57] When the organism is sensitive, any of these drugs can be used for the treatment of these conditions. Oral amoxicillin 50–75 mg/kg/day for one week after the first negative blood culture and defervescence is preferred for the treatment of patients with infection due to susceptible Salmonella. Defervescence may be rapid and relapses may be slightly less frequent with amoxicillin than with chloramphenicol.[1] Considerable experience with the use of amoxicillin in the treatment of this disease in children has been acquired.[134]

Chloramphenicol and sulfonamides should be used with caution in patients who have glucose-6-phosphate dehydrogenase deficiency, as some synergy in precipitating hemolysis is seen between drug and disease.[180]

Whatever treatment is used, reasonable isolation procedures, source detection and case-finding, and followup are required. Relapses are usually seen 8–10 days after cessation of a 2-week antibiotic therapy course.[262]

Prevention

Improved hygiene, sewage facilities, and food handling and preparation are integral measures toward controlling typhoid and enteric fevers in most communities. Immunization is useful for travelers but cannot be relied on to prevent disease when the subject ingests large numbers of bacteria. A new oral vaccine, Ty21a, shows much promise of improving protection for children in endemic areas, as a 96% efficacy rate has been demonstrated.[313] Nevertheless, vaccine failures constitute an argument against complete reliance on this method of prevention.[128]

Bacteremia/Septicemia

Epidemiology/Etiology/Pathogenesis

Pneumococcal and *Haemophilus influenzae* bacteremia are among the most common forms of nonlocalized bacterial infection in normal children.[12] Staphylococci and enteric bacteria need to be added to this list in patients who acquire bacteremia in hospital,[343] and Salmonella bacteremia (enteric fever) in many developing countries. Localized infections as a result of these bacteremias include cellulitis, pneumonia, meningitis, osteomyelitis, arthritis, and sinusitis. Frequently, however, fever is the only sign of bacteremia, especially in infants 3 months to 2 years of age. Pneumococcal and Haemophilus infections are rare in newborns, in whom they have many features in common with early-onset group B streptococcal infection.[25] Patients with underlying gastrointestinal and respiratory conditions, sinusitis, and immunodeficiencies may also have anaerobic bacteremia.[31]

The pathogenesis of many of these bacteremias is unclear, although in newborns, relative immunodeficiency and exposure to pathogens in the maternal and nursery environments are contributory. In other cases, such as patients with hemoglobinopathies, including sickle cell disease[263] and sickle cell-C disease,[35] hyposplenism may be an important predisposing factor. In fact, patients with absent or dysfunctional spleens are not only at risk for bacteremia but are also more likely to have fulminant complications, including hypotensive shock and disseminated intravascular coagulation.[192] This emphasizes the need for suspecting bacteremia early in such patients, and instituting appropriate evaluation and treatment.[274] Because of this risk, penicillin prophylaxis (phenoxymethyl penicillin 250 mg PO b.i.d.) is recommended for all such children until they reach 6 years, or for approximately 1 year after splenectomy in patients above this age. Pneumococcal vaccine should be added in patients above 6 months of age, and a booster dose administered at age 2 years.[274] This program does not provide complete protection and parents need to be warned to seek medical care (for appropriate cultures and antibiotics) early in the course of fever.

Bacteremia can occur after dental procedures, particularly if anesthetics and intubation are used,[11] and as many as 30% of children may have transient bacteremia with *Streptococcus viridans* after tooth extraction.[302] Other predisposing procedures include endoscopy,[238] bronchoscopy,[3] and nasotracheal suctioning.[185] Polymicrobial bacteremia may be due to trauma, immune deficiency, or child abuse.[190] Suffice it to say that any invasive manipulation that causes bleeding and disturbs the integrity of mucosa or skin may have associated bacteremia. These are generally inconsequential, except in patients with underlying cardiac disease or immune deficiencies. The source of the common types of bacteremia, such as Haemophilus and pneumococcus, are probably related to respiratory colonization with concomitant or prior viral infection.

Remember that helminthic and protozoal infections, such as filariasis and malaria, are common causes of febrile septicemia in many parts of the world, and require direct examination of blood films for appropriate diagnosis. Generally speaking viral infections, such as those due to enteroviruses and adenoviruses, probably account for more acute undifferentiated febrile illnesses than do bacterial, protozoal, or helminthic infections combined, particularly in industrialized countries. Mycotic, mycoplasmal and chlamydial infections may also be important. In some hosts, such as patients with sickle-cell disease, viral infections (e.g., parvovirus) may trigger aplastic crises.[293] Rickettsioses need to be added to the causes of fever in appropriate seasons in endemic regions, and fungemias in appropriate hosts with predisposing conditions.

Clinical Manifestations

In some patients fever may be the only manifestation of bacteremia. In other patients, localizing signs, as discussed in other chapters, include cellulitis, pneumonia, and meningitis. The same causative microorganisms, such as meningococci, may lead to fulminant sepsis in some patients, and mild,[239] or even unsuspected bacteremia,[56] in others. The presence of splenomegaly is suggestive of several acute and chronic infections (Table 12–4). Some patients with pneumococcal bacteremia have been noted to have cystic gingival swellings associated with positive blood cultures.[351]

Chills, malaise, sweating, headache, abdominal pain, myalgia, and arthralgia may be present in patients with bacteremia. Meningococcemia should be suspected in any child with a petechial or purpuric rash, (Fig. 12–1), even though the distribution may suggest other diagnoses, such

TABLE 12-4. Infectious Causes of Splenomegaly

Malaria
Schistosomiasis
Infectious mononucleosis
Cytomegalovirus infection
Brucellosis
Endocarditis
Histoplasmosis
Tuberculosis
Splenic abscess
Leishmaniasis
Acute sepsis

as anaphylactoid purpura.[281] Shock may be seen with bacteremia, especially that due to meningococcus. Acute respiratory failure may also occur,[132] as may massive hemolysis with clostridial sepsis.[316]

Diagnosis

Bacteremia can be diagnosed specifically only by appropriate microbiologic culture, although its presence can be inferred from clinical (e.g., meningitis) and laboratory (e.g., presence of bacterial antigen in serum) features. Certain signs may be helpful in indicating the need for blood cultures. Among these, the white blood cell count and erythrocyte sedimentation rate are most useful, particularly in the first 2 years of life. In the first 2 months of life, leukopenia (< 5000 white blood cells/mm^3) or leukocytosis ($> 20{,}000$ white blood cells/mm^3) and other laboratory indicators (immature neutrophils/total neutrophils ≥ 0.2, erythrocyte sedi-

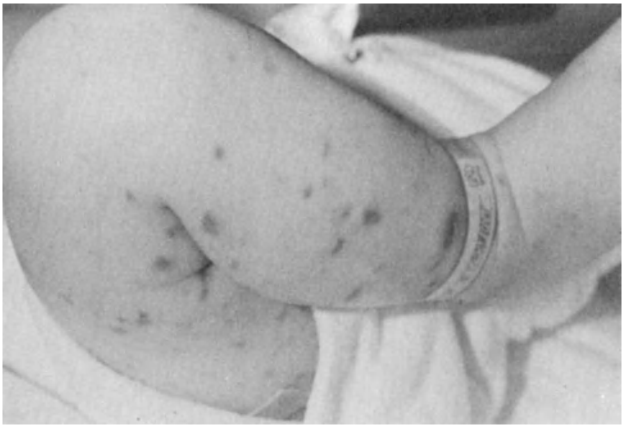

Figure 12-1. Purpuric rash of meningococcemia.

mentation rate > 15 mm/h, positive C-reaction protein latex-agglutination test, positive haptoglobin latex agglutination test) may also be important.[253] The combination of a WBC count of 20,000/mm^3 or more and a temperature of 39.5°C or higher is associated with an increased likelihood of bacteremia in children with sickle-cell hemoglobinopathy.[177]

If sepsis is highly suspected, methylene blue or gram stain examination of the buffy coat may provide rapid and direct evidence of this diagnosis.[270]

Blood culture techniques should be meticulous both at the bedside and in the laboratory. The skin is first cleaned with 70% alcohol solution, which acts both as a solvent and a germicidal agent. Povidone-iodine is then applied topically and allowed to dry. Alternatively, tincture of iodine can be used, providing it is washed off with alcohol after the blood culture is obtained. If a skin bacterium is suspected as a cause of the bacteremia (staphylococci, diphtheroids,[195] etc.) or skin lesions are present (remember, patients with eczema, pyoderma, burns, casts, etc. may have atypical skin flora) obtain a culture of the prepared skin before venipuncture (Fig. 12–2). The venipuncture is then performed with aseptic technique and a new needle is used to inoculate the blood culture bottles. Inoculation of two blood culture bottles will allow incubation of one aerobically (more likely to grow Pseudomonas, Brucella, etc.) and one anaerobically.[314] A second blood culture after surgical and other manipulative procedures (e.g., debridement, aspiration, biopsy, endoscopy, etc.) may increase the chances of diagnosis of bacteremia associated with focal lesions. Communication with the microbiology laboratory is important, since special media, advantageous for the isolation of fungi, Brucella, *Francisella tularensis,* viruses, and other agents, and antibiotic removal devices may be required.[8]

What does bacteremia mean? This depends on the age of the patient, underlying disease, and the qualities and features of the bacteria found in the blood. Among these, high concentrations of bacteria are often associated with serious focal infections,[309] and polymicrobial bacteremia may be associated with malignancies, burns, decubitus ulcers, and neurologic illness.[280]

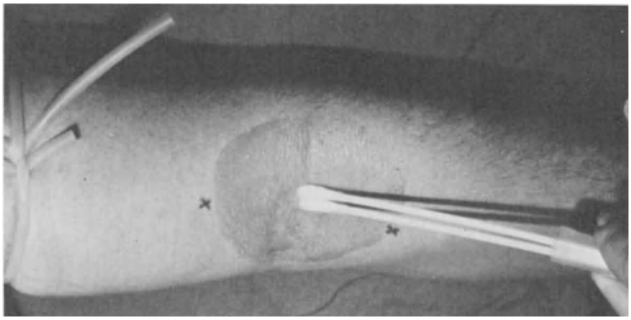

Figure 12–2. Culture of prepared skin may help interpretation of blood culture results in selected cases. (Courtesy of Dr. G. Burgess.)

Treatment

There are two ways to approach the treatment of nonlocalized bacteremia in young infants. Some use expectant antibiotic (e.g., amoxicillin 100 mg/kg/day PO) therapy in febrile infants in the first 2 years of life with white blood cell counts above 15,000/mm^3 and elevated sedimentation rates (greater than 30 mm/h), pending the results of blood, cerebrospinal fluid, and urine cultures.[40] Sometimes, unsuspected meningococcemia can be effectively treated in this way.[90] Others prefer to observe these patients without therapy for 24–48 h, either in hospital or at home. If bacteremia is diagnosed microbiologically during this time, the patient is recalled immediately. A repeat blood culture and lumbar puncture are indicated in almost all cases. Other cultures depend on localization, if any has developed. Intravenous ampicillin 200 mg/kg/day, divided every 6 h, or oral chloramphenicol 75 mg/kg/day should then be initiated, depending on susceptibility studies and the results of repeat cultures (intravenous cefotaxime 150 mg/kg/day, divided q 8 h, may also be used). If these cultures subsequently prove to be negative and the patient remains well, he can be discharged. If cultures are positive, then a search for locus of infection and continued antibiotic therapy for at least 1 week are indicated. Many patients do have self-limited bacteremias, however, there is no known way to differentiate those at risk for continued and progressive infection from those who will have a benign course.[29] In fact, several patients have been noted to develop meningitis, pneumonia, and arthritis after bacteremia has been treated with oral, and even intramuscular, antibiotics.[206] Meningococcal and other infections, caused by acute and convalescent complications (due to infectious and immunopathic mechanisms) can include endophthalmitis, aseptic meningitis, pericarditis, arthritis and phlebitis.[306]

Septic Shock

Etiology/Pathogenesis

A variety of infectious conditions may be associated with shock. Some are directly related to the infection, such as the release of endotoxin during gram-negative bacteremia, or the activation of complement by viruses, such as dengue.[310] In others, reactions to treatment, such as anaphylaxis, the Jarish-Herxeimer reaction, and organ dysfunction (e.g., cardiac failure due to the late effects of viral myocarditis) are responsible. A syndrome of hemorrhagic shock, fever, encephalopathy, and hepatic and renal dysfunction, without evidence of specific cause, has also recently been described in England.[186] Gram-positive bacteria contain endotoxin-like substances which can also lead to clinical syndromes indistinguishable from shock due to gram-negative organisms. Examples include early-onset group B streptococcal septicemia and some cases of pneumococcal and staphylococcal infections. Noninfectious causes of shock include hypovolemia due to bleeding, dehydration, ingestion of drugs and other toxins, and myocardial infarction.[248]

The pathogenesis of shock is complicated and multifactorial. Endotoxin or endotoxin-like substances induce widespread vasculitis and the release of thromboplastins, prostaglandins,[141] and β-endorphins. Complement and serotonin also contribute to the pathogenesis of septic shock.[202] Hepatic, cerebral, and renal injuries are secondary to both the direct effects of endotoxin and to decreased blood flow and hypoxia.

Many infants and children are seen with early shock states. Their amazing recuperative powers are often demonstrated by a rapid response to fluid replacement in various states of dehydration.[229] After all, these conditions represent hypovolemia, and many of the associated signs and symptoms are referable to decreased perfusion and the secondary effects of a contracted intravascular volume. Yet, these young infants rarely develop progressive shock and, even less commonly, irreversible shock. Nonetheless, recovery depends on fluid replacement and competent renal and cardiovascular systems. Hence, some of the complications of shock (thrombosis, renal failure) are occasionally seen in severe dehydration due to gastroenteritis, or with anorexia and vomiting due to other infectious diseases or antimicrobial therapy.

Diagnosis/Clinical Manifestations (Table 12–5)

The diagnosis of septic shock can easily be missed in its early stages. Patients with septicemia, pyelonephritis, pelvic inflammatory disease, surgery, and burns should be watched very closely for the early signs of shock. I include patients with meningitis and suspected bacteremia, and those with some viremias and rickettsial infections in this group as well.

The key to successful management of shock depends on early diagnosis. The best clues are provided by frequent (e.g., every 15 min) blood pressure and pulse monitoring. As with dehydration, adequate fluid replacement in the early stages will prevent hypotensive shock in most cases. If these patients are stable over a 4–8 h period, then vital signs may be monitored less frequently. It is rare for patients receiving adequate fluids and appropriate antimicrobial therapy to deteriorate into a state of shock after the first 12–15 h of such therapy. This is the critical period of monitoring that needs to be stressed, despite the apparent state of well being of patients with many of the infections that can predispose to septic shock.

In the early stages of shock, laboratory abnormalities may include hypoxemia, respiratory alkalosis, metabolic acidosis, and hyperglycemia. In later stages, hypoglycemia, and coagulopathy are also often present.[249]

TABLE 12-5. Stages of Septic Shock

- I. Warm Phase/High Output
  - Increased cardiac output
  - Increased pulse pressure
  - Increased systolic blood pressure
  - Tachycardia
  - Tachypnea
  - Warm/flushed skin
  - Alert/apprehensive/confused
  - Normal or decreased urine output
- II. Cold Phase/Low Output
  - Decreased cardiac output
  - Decreased pulse pressure
  - Decreased systolic and diastolic blood pressure
  - Cold/pale skin
  - Disoriented → semicoma
  - Decreased urine output
- III. Irreversible Shock
  - Decreased cardiac output
  - Increased pulse pressure
  - Decreased systolic blood pressure
  - Absent diastolic pressure
  - Purpuric skin lesions
  - Coma
  - Anuria

When shock is diagnosed in the cold phase, it is often too late to reverse it. There is no strict definition of irreversible shock, but permanent vascular damage tends to occur in patients with extensive purpura, and prolonged hypoxemia, acidemia, and anuria.

Treatment

The most important factor in the treatment of all stages of shock is correction of intravascular hypovolemia. Regardless of the etiology, patients with hypotensive shock should receive fluids as quickly as possible. Patients who have bled do best with whole blood replacement, and patients with evidence of coagulopathy may do best with fresh frozen plasma infusions. Do not delay! Until these fluids become available Ringer's lactate or 0.9% sodium chloride should be administered intravenously. Many patients with high output, warm shock will respond quickly to approximately 20 ml/kg of such fluids administered over a 20–30-min

TABLE 12–6. Patient Monitors in the Management of Stage II (Low-Output) Septic Shock

Pulse/electrocardiograph (continuous with recording)
Two intravenous infusions
Urinary catheter
Central venous pressure or pulmonary artery Swan-Ganz catheter
Arterial catheter for continuous blood pressure monitoring and for blood gas and pH sampling
Thermistor probe for frequent (or continuous) core temperature measurement

period. Next, the more appropriate fluids can be administered, depending on the etiology of the shock.[249] This approach may have to be modified in newborns, in whom exchange transfusion may best remedy hypovolemia, acid-base imbalance, coagulopathy, and other metabolic disturbances, as well as remove a considerable load of bacteria and/or toxin(s).[244]

Shock is a dynamic event requiring intensive evaluation and management. If initial fluid replacement is not associated with improvement in blood pressure, pulse, and acid-base balance, then fluid replacement should be continued and a more aggressive monitoring and treatment program initiated (Table 12–6). This should include continuous monitoring of vital signs and establishment of adequate routes for fluid replacement and for obtaining vital sign measurements.[350] After the patient has reached the advanced stages of shock, it may be too late to find for the usual infusion sites, since peripheral venous collapse may occur.

TABLE 12–7. Treatment of Septic Shock

Cardiorespiratory support
Fluids, IV: 10–20 ml/kg maintain central venous pressure > 10 mm Hg
or
Pulmonary wedge pressure ≥ 12 mm Hg
Maintain hematocrit 35–40%
Antibiotics, IV
Correction of acid-base/electrolyte/glucose/mineral (calcium) abnormalities
Surgical drainage and relief of obstruction
Dopamine 1–25 ug/kg/min IV infusion, until blood pressure rises and urine output increases (aim for > 0.7 ml/kg/h)
Corticosteroids
  e.g., methylprednisolone 30–60 mg/kg IV every 2–4 h until blood pressure rises
J5 antiserum 3 mg/kg IV (not commercially available)

Hence, establishment of large and duplicate infusion sites early is important.

The treatment of septic shock should be initiated and maintained, simultaneously with the establishment of infusion sites and monitoring devices (Table 12–7). Cardiorespiratory support and fluid management are of paramount importance. Next in line are appropriate antibiotics by the intravenous route; correction of acid-base balance, electrolyte, and glucose derangements; and appropriate surgical drainage of focal infections and/or removal of foreign bodies and obstructions.

When patients are still refractory to treatment at this stage, use of pharmacologic agents should be considered. A common error in the diagnosis and management of shock is the early prescription of vasoactive and cardiotropic drugs without adequate steps for monitoring and treating cardiorespiratory and fluid abnormalities. All of the steroids and catecholamines in the world will not help patients who remain hypovolemic and hypoxemic!

In order of priority, dopamine is at present the β-adrenergic stimulator of choice in the treatment of persistent hypotension in the face of septic shock caused by gram-negative organisms. This drug will increase myocardial contractility, heart rate, coronary blood flow, renal blood flow, and cardiac output. The drug is remarkably safe in low doses, although the therapeutic/toxic ratio may be low. For example, doses greater than 10 ug/kg/min can stimulate α-adrenergic receptors leading to vasoconstriction, ischemia, and even peripheral gangrene.[198] If ischemia develops, phentolamine or chlorpromazine should be infused in an attempt to reverse the vasoconstriction.

The use of adrenal corticosteroids in septic shock remains controversial.[125] Nonetheless, if they are chosen, administration should be started early and high doses used. These doses (Table 12–7) should be repeated every 2–4 h as long as the patient is hypotensive or in the stage of hyperdynamic high-output shock. The risks begin to outweigh the benefits if corticosteroids are continued beyond this stage.[166] Experimental studies indicate, in fact, that the efficacy of corticosteroids in shock is seen over a narrow dose range, often impossible to predict in an individual patient.[107] Corticosteroids do not benefit patients with dengue shock syndrome.[310]

Newer approaches to therapy include the use of human antiserum prepared against core glycolipid antibody (J5 antiserum) in a dose of 3 ml/kg intravenously.[354] This treatment has effectively decreased by one-half the mortality rate in adults with gram-negative septicemia. Although investigational, this adjunct holds promise for application in a wide variety of patients with endotoxic shock. In consideration of the pathogenesis of septic shock, prostaglandin inhibitors (such as ibuprofen[141] and indomethacin[202]) and β-endorphin inhibitors, such as naloxone,[65] have been used experimentally and hold promise for future application.[251]

Prognosis

Shock is a grave complication of bacteremia and sepsis because of widespread vascular injury and its effects on many organs. Patients with disseminated intravascular coagulation, central nervous system anoxia, and prolonged periods of refractory hypotension do least well. Permanent renal, myocardial, and central nervous system injury can result. Shock lung,[237] congestive heart failure, and myocardial ischemia may also be problems during early convalescence. Patients who respond quickly during the warm hyperdynamic phase of shock usually recover completely.

Infectious Mononucleosis and Other Epstein-Barr Virus Infections

Epidemiology/Etiology

Infectious mononucleosis is a syndrome most commonly due to Epstein-Barr virus infection of B lymphocytes.[6] If the host is immunologically normal at the time of infection, the resulting immune regulatory dysfunctions are transient and the disease is benign and self-limited. If, however, the host is immunologically abnormal, severe consequences may occur, including chronic infection and death. The infection is seen in individuals of all ages, although it is most commonly symptomatic in school-aged children and adolescents. Although rare in pregnancy[184] primary Epstein-Barr virus infection has been implicated as a cause of multiple congenital abnormalities.[101]

The infection is usually spread by intimate and prolonged contact and virus is mostly concentrated in upper respiratory salivary secretions. Transmission after blood transfusion has also been reported.[324] Rarely, cytomegalovirus[70] and Toxoplasma infections can cause similar syndromes.[133]

Clinical Manifestations

Infectious mononucleosis often presents as persistent fever. The incubation period is estimated to be between 4 and 6 weeks, but the expression of disease is diverse and diagnosis is often difficult (Table 12–8). The classic features of disease (fever, lymphadenopathy, sore throat, and rash) are less frequently seen in children under the age of 6 years, in whom Epstein-Barr virus infection is commonly asymptomatic.[6] Although exudative pharyngitis and cervical lymphadenitis (often nontender) are frequent in this disease, these are not usually due to Streptococcus.[146] Hepatic involvement is extremely variable and some patients may be jaundiced; hepatic necrosis has also occurred. Skin manifestations are

TABLE 12–8. Clinical Manifestations of Infectious Mononucleosis

- Fever
- Pharyngitis
- Lymphadenopathy
- Rash
- Hepatitis
- Splenomegaly
- Pneumonia
- Neurologic
  - Encephalitis
  - Meningitis
  - Transverse myelitis
  - Guillain-Barré syndrome
  - Bell palsy
- Arthritis

diverse and include urticaria, sometimes in response to exposure to cold,[348] erythema nodosum,[23] or a diffuse maculopapular nonpruritic rash when the patient is receiving penicillin or ampicillin (Fig. 12–3).[130] Rarely, patients describe visual distortions called the "Alice in Wonderland syndrome".[285] Other neurologic manifestations have also been reported, and Epstein-Barr virus has been isolated from the cerebrospinal fluid of a patient with meningitis.[112]

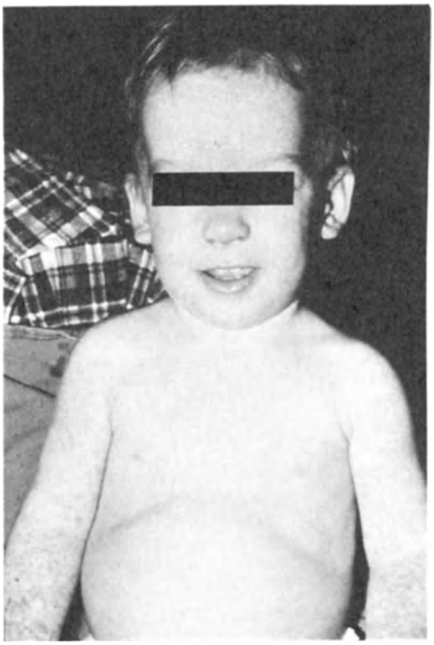

Figure 12–3. Skin eruption after the administration of ampicillin in a patient with infectious mononucleosis. For color reproduction of this figure see frontmatter.

In addition to the above features, patients with infectious mononucleosis may have a variety of clinical complications and laboratory abnormalities (Table 12–9). These include immunologic disturbances,[130] hematologic abnormalities, severe dysphagia and anorexia, airway obstruction, and pulmonary embolism.

Epstein-Barr virus most commonly causes infectious mononucleosis but has also been implicated in the pathogenesis of Burkitt lymphoma, nasopharyngeal carcinoma and sarcomas in transplant recipients. The virus has also been associated with arthritis, pneumonia, pancreatitis, hepatitis, and proctitis[173] and can cause illness that mimics the clinical and hematologic findings in juvenile chronic myelogenous leukemia.[121]

Diagnosis

Diagnosis of the infectious mononucleosis syndrome is based on clinical, hematologic, and serologic criteria. The presence of heterophile antibody (after absorption with guinea pig red blood cells) in patients with appropriate clinical signs and symptoms is sufficient for the diagnosis in most cases. A rapid slide agglutination method, (using sensitized horse red blood cells), the Monospot test, is very useful for screening for these antibodies; however, false-positive results have been reported (Table 12–10). Heterophile antibody may not be detected in up to 60% of children under 6 years of age with infectious mononucleosis, however, Epstein-Barr virus serology is usually positive.[318] It should also be remembered that the heterophile antibody test may remain positive for a year or longer after convalescence.[77]

The presence of serum IgM antibody against Epstein-Barr virus capsid antigen is diagnostic of active infection, although this antibody response may be present only from the 3rd to the 11th week of the illness.[175]

Peripheral lymphocytosis (atypical lymphocytes) is also a hallmark of

TABLE 12–9. Laboratory Features of Infectious Mononucleosis

Auto-immune antibodies[130]
Leukocytosis
Lymphocytosis
Heterophile antibody
IgM anti-EB virus capsid antigen
IgG anti-EB ≥ 1/80
Thrombocytopenia
Anemia
  Hemolytic[247]
  Aplastic[182]
Neutropenia[234]
Anergy[110]

TABLE 12–10. Causes of False-Positive Monospot® Test

Hepatitis
Lymphoma
Leukemia
Cytomegalovirus infection
Adenovirus
Rubella
Mumps
Malaria
Carcinoma
Systemic lupus erythematosus[120]

this disease, but, like the presence of heterophile antibody, may be found only in older children and may not be specific. The effects of Epstein-Barr virus infection on the quantities of leukocytes and lymphocytes in infectious mononucleosis in children are impressive.[85]

Treatment

Many young children with infectious mononucleosis are asymptomatic, and the condition is benign and self-limited in most older patients. Rest and administration of antipyretics usually suffice as therapy. Patients with severe pharyngitis, incapacitating malaise, anorexia, and fatigue, and/or those with obstructive respiratory symptoms may be transiently improved by the systemic administration of corticosteroids. This should not be done without careful consideration of the risks, however, considering the diverse and broad immunologic disturbances associated with this infection. Although nonblinded preliminary studies suggest that metronidazole may be useful,[117] this therapy has little theoretic basis, and these observations require confirmation. Similarly, preliminary results of acyclovir therapy have been encouraging.[301]

Isolation of these patients in hospital, and in the community, should reflect the fact that infection is usually due to prolonged and intimate exposure to virus in the patient's saliva. The spread is slow and the expression of disease generally benign. Close contacts may not exhibit infection until 2 or 3 months after exposure.[236] In a study of family spread, 20% of households had serologic evidence of Epstein-Barr virus infection, but only 6% of the contacts developed symptomatic disease.[86]

Prognosis

Infectious mononucleosis is generally a benign condition. Nevertheless, severe consequences have been noted due to this and related Epstein-Barr virus infections. Patients with infectious mononucleosis have died as a consequence of respiratory obstruction, central nervous system involvement, hepatic necrosis,[41] pulmonary embolism, and the development of malignant lymphomas. Rupture of the spleen has also been seen up to 3 months after the onset of illness, prompting recommendations that athletes involved in body contact sports not resume these activities for this time period.[283]

A particularly virulent Epstein-Barr virus infection has been described in male members of certain families.[266] These patients may develop fatal or chronic infection, hypogammaglobulinemia, progressive combined variable immunodeficiency, aplastic anemia, and malignant B-cell lymphomas.[2] This Epstein-Barr virus infection has also been described in a non-X-linked recessive inheritance pattern in children with defective natural killer cells[87] and in patients with hypogammaglobulinemia.[10]

Epstein-Barr virus infection also plays an important role in the etiology of Burkitt lymphoma and nasopharyngeal carcinoma, and may predispose the patient to other malignancies,[243] although the exact pathogenesis is unclear. It can also be a rare cause of myocarditis[273] and hemophagocytic syndromes. Despite these rare, but serious, manifestations, the vast majority of infants and children who seroconvert to Epstein-Barr virus remain asymptomatic,[311] yet transient cellular and humoral immune suppression may result.[26]

Permanent immunity is usually a result of infectious mononucleosis, although recurrent cases have been described.[216] These probably represent persistent infection, rather than recurrent disease.[118]

Leptospirosis

Epidemiology/Etiology

Leptospira are spirochetes that chronically infect rodents and dogs and can be excreted in their urine. Man acquires this infection by exposure to urine, or to water contaminated with urine, from these sources, and from swine, cattle, and other mammals. Most cases are seen in rural areas in the spring and fall; however, children living in urban areas are certainly at some risk.[346] Outbreaks in fish farmers and other individuals exposed to rat-infested water have recently been reported.[276] Approximately 100–150 cases are still seen in the United States per year, with two to five deaths. Worldwide, this infection remains an important cause of morbidity and mortality, since these spirochetes can invade almost any organ in the body.

Many serotypes are involved, most commonly *Leptospira interrogans* serotypes *icterohaemorrhagiae, canicola,* and *autumnalis.*[82]

Clinical Manifestations

The disease resembles many others, especially aseptic meningitis, hepatitis, encephalitis, pneumonia, and the mucocutaneous lymph node syndrome.[82] The condition may also present as fever of unknown origin. A bacteremic phase is followed by a phase of urinary excretion. During either of these, the patient may manifest fever, headache, chills, myalgia,[60] and maculopapular rash, which sometimes desquamates.[346] A specific constellation of fever, jaundice, and conjunctivitis due to leptospira is called Weil disease. Other manifestations may include renal dysfunction with azotemia and oliguria, cholecystitis, pancreatitis, and mucocutaneous lesions.

Diagnosis

Epidemiologic history and fever, hepatomegaly, conjunctivitis, and rash may suggest the diagnosis. Alternatively, the patient may have neck stiffness and present with aseptic meningitis. Since this most commonly occurs during the warm months of the year, it is easy to confuse infection due to leptospira with enteroviral causes of this syndrome.

Although these spirochetes may be seen by dark-field examination of the urine, cerebrospinal fluid, or blood, this test is rarely fruitful, since very high concentrations of bacteria are required for visualization and red cell fragments and other debris may be mistaken for bacteria. It is necessary to inoculate specimens on special media, such as Fletcher's semisolid medium, and to incubate cultures in the dark at 30°C for approximately 5–6 weeks.

Most of the diagnoses are made serologically by a slide agglutination test, and titers confirmed by a microagglutination method. Positive cultures and/or a fourfold rise in antibody, or a single titer greater than 1/100 with an appropriate clinical syndrome, are diagnostic. Blood cultures are most useful in the first week of illness, although patients rarely present at this time. Thereafter, urine cultures are best, since the organism may be excreted in the urine for up to 1 month. Many leptospirosis patients also have pyuria at this time.[346]

Treatment

Although spirochetes are generally sensitive to penicillin, there are few published data that convince one of the dramatic effects of this therapy after the first week of illness.[60] Nevertheless, rest, supportive care, and aqueous penicillin G 100,000 units/kg/day treatment are recommended. When meningitis is present, larger doses may be used. Therapy for 7–10 days is probably sufficient. Leptospirosis is generally a benign disease, but fatalities can occur with central nervous system and severe hepatic involvement. Unfortunately, little specific therapy is available for these complications. Hygienic and public health measures are reducing the incidence of disease markedly in industrialized countries.

Brucellosis

Etiology/Pathogenesis

Brucellosis is an infection of decreasing importance in the United States,[352] as improvements in the health care of domestic and farm animals occur, but it remains a great problem worldwide. There are four species of Brucella, a gram-negative bacillus: *Brucella melitensis* (goats are the major reservoir), *B. abortus* (cattle), *B. suis* (swine), and *B. canis* (dogs). Man acquires infection by eating infected animal tissue or products, such as cheese, raw milk, and, occasionally, by mucosal or percutaneous inoculation of bacteria after contact with infected tissues or hides. Transmission by bone marrow transplantation has also been reported.[231] Infection is more commonly seen in adults, since it is an occupational hazard of farmers, abattoir workers, and veterinarians.

Clinical Manifestations

The diagnosis is not simple, since the signs are rarely specific. Fever, chills, weakness, backache, headache, arthralgia, and malaise are common. Some of these patients present with fever of unknown origin. Lymphadenopathy and hepatosplenomegaly are frequently present, as is anemia, but none of these are diagnostic. Approximately 10% of patients have skin manifestations, including macules, vesicles, cutaneous and subcutaneous papules,[95] and erythema nodosum.[18] Septic[321] and postinfectious[104] arthritis, and abortion,[286] are rare in brucellosis. Sacroiliac pain in patients with brucellosis may indicate the presence of Brucella sacroileitis.[235]

Brucella infection has a hematogenous phase, during which the bacteria may localize in almost any site in the body, leading to meningitis, endocarditis, focal abscesses, and osteomyelitis.[59] The disease and its complications are uncommon in the pediatric age group.

Diagnosis

Diagnosis depends on epidemiologic history, culture of the bacteria, and/or serology. This is a relatively strict aerobic bacteria that is somewhat fastidious in its requirements. Hence, communication with the microbiology laboratory when this diagnosis is suspected may improve the yield by use of aerobic incubation and enriched Brucella media. The diagnosis is more often made by detection of serum agglutinins to Brucella antigen. *Brucella abortus* antigen is most commonly used in North America, since it cross-reacts with *B. suis* and *B. melitensis*. If one is looking for *B. canis* antibody, however, a specific antigen is required.

Treatment

The literature is replete with recommendations for different drugs, dosages, and durations, probably reflective of the self-limited nature of this infection, and the dearth of controlled studies. However, chronicity and persistent intracellular survival are features of the relationship of Brucella with the host. Classically, tetracycline and streptomycin have been used, as has sulfadiazine or ampicillin.[81] The duration of therapy has generally been 3–4 weeks. More recently, rifampin[191] and trimethoprim-sulfamethoxazole have also been used, alone and in combination.[59] Some of the new cephalosporin derivatives, such as moxalactam, may also be effective.[321] Surgical drainage is an important adjunct in patients with focal infections. Although rare, this infection is likely to become chronic and debilitating in some patients and requires aggressive and prolonged therapy, as well as followup to document sterilization and permanent cure.

Tularemia

Epidemiology

Tularemia is seen in many parts of the world, particularly during warm seasons. Human infection is associated with contact with domestic and wild animals, and with insect vectors. Rabbits, hares, muskrats, squirrels, voles, and other rodents are most commonly infected; however, a large number of animal species may carry these bacteria,[75] including domestic animals and even household pets such as dogs and cats.[76] Animals in zoos may also be involved, as noted by several cases in nonhuman primates.[232] Contact may be either direct, with animal tissues or secretions through bites or scratches, or indirect, in which case the bacteria may be carried by insect vectors, including wood ticks and deer flies.[303] In the United States, disease has been encountered in most parts of the country, although it is most prevalent in the warmer southern states and in rural areas where farming and hunting are more popular.

Etiology

This infection is caused by small, fastidious, gram-negative coccobacilli, *Francisella tularensis*. The organism is highly infectious and extreme caution

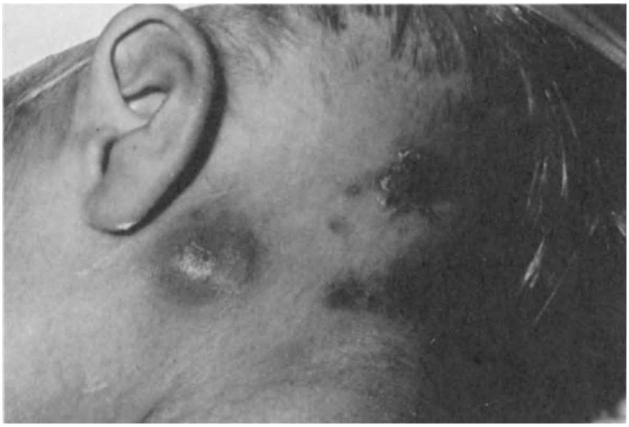

Figure 12–4. Tularemic lymphadenitis.

is necessary if it is suspected in laboratory culture material or infected animal carcasses or skins. *F. tularensis* type A is most prevalent in North America, and is more virulent than type B strains.[288]

Clinical Manifestations

The most common form of tularemia is localized lymphadenopathy (Fig. 12–4), often in association with an ulcerated papule at the site of inoculation of the organism (through tick bite, animal bite, or scratch). The site of inoculation will often determine the clinical expression; hence eye, throat, or pulmonary infection can be seen (Table 12–11). The lymphatic form is usually diagnosed after nodular swelling has persisted for 1–2 weeks. The inoculation papule and regional lymph nodes are often nontender, although suppuration and tenderness may occur later. Some patients may have a typhoidal syndrome with generalized lymphadenopathy and splenomegaly. The typhoidal form of disease is most difficult to diagnose, since fever and malaise are present, but there may be no localizing signs. In such cases, the diagnosis is usually dependent on a

TABLE 12–11. Clinical Manifestations of Tularemia

Ulceroglandular
Oculoglandular
Pharyngeal
Typhoidal
Pneumonia

history of contact. Pneumonia occurs secondary to bacteremia in 10–15% of ulceroglandular tularemia and in 30% of typhoidal cases.[288] Liver involvement may rarely be seen in patients with systemic infection.[207]

Pharyngitis may be exudative, suggesting streptococcal disease, infectious mononucleosis, or diphtheria.[325] Eye involvement can be severe and includes conjunctivitis, keratitis, and periorbital cellulitis.[109] Preauricular lymphadenopathy and systemic fever may also be present. Infectiousness of this organism is attested to by a case in which blood from an infected tick was accidentally squirted into the patient's eye. Fulminant oculoglandular disease developed, despite the application of four topical antibiotic ophthalmic medications.[109]

Diagnosis

Tularemia is difficult to diagnose unless a papule is present and/or a history of tick bite or appropriate animal exposure is obtained. In North America, rabbit hunters account for approximately two-thirds of cases, although outbreaks have been reported in association with other exposures. There is no rapid way to make the diagnosis unless the patient has already been ill for approximately 2–3 weeks. In such cases, the serum agglutination titer for tularemia should be at least 1/80. A sequential rise in titer is even more diagnostic, since there are some cross-reactions with Brucella, heterophile antibody, and OX19 antibody. Although a skin test has been described that becomes positive by the end of the first week of illness, this is not commercially available.[34] The organism may be cultured on blood agar enriched with glucose and cystine; however, storage of materials in biologic safety cabinets and scrupulous aseptic techniques are necessary to avoid infection of laboratory personnel. Moreover, growth of the organisms may require up to a week of incubation and the bacteria are often difficult to identify.

Treatment

These bacteria are usually resistant to penicillin, cephalosporins and erythromycin. The diagnosis is often first suspected when patients with regional lymphadenopathy fail to respond to one or more of these antimicrobials. When the diagnosis is made, the patient with mild and/or localized infection can be treated with tetracycline or chloramphenicol, both effective, but bacteriostatic, against these bacteria. Some relapses have been seen. Bactericidal activity and rapid clinical improvement are seen with use of the aminoglycosides, including streptomycin and gentamicin. Although most experience has been gained with streptomycin, gentamicin, tobramycin, and kanamycin are also effective.[208] Conventional doses for approximately 10 days are used.

Prevention

Knowledge of the ecology of these bacteria should prompt appropriate preventive action for hunters, animal skinners, and the like. Considering the wide number of animals that can be infected and the prevalence of insect vectors, the disease is almost impossible to avoid. Hence, large outbreaks in certain countries with high enzootic activity are seen. A live attenuated vaccine has been used in the U.S.S.R.; however, boosters are required every 5 years and there is little experience with this product in other parts of the world.[171]

Plague

Epidemiology/Etiology

The word plague strikes fear into the hearts of many. It is no wonder, in consideration of the virulence of this organism and its propensity for epidemic spread with attendant high mortality. Infection is due to *Yersinia pestis*, a gram-negative bacillus, that circulates in the bloodstreams of infected rodents, prairie dogs, rabbits (and, occasionally, squirrels) and is transmitted to man by flea bite. Infected fleas can be carried into the home on domestic dogs and cats as well.[328]

The disease is rampant in Africa, Asia, and South America, although it is occasionally seen in the United States, where it is restricted to the western states (New Mexico, Arizona, Colorado, Utah, Nevada, California, Oregon, and Wyoming). In fact, of the cases reported in the U.S. in the last 10 years, two-thirds have come from New Mexico.[204] In the United States, where approximately 15–20 cases/year occur, the group most frequently affected were children under 16 years of age. Even newborns can be infected under appropriate epidemiologic conditions.[337]

Clinical Manifestations

Plague resembles tularemia in many ways. Not only do the causative organisms look alike on gram stain, but they both cause septicemia, pneumonia, and lymphadenopathy syndromes. Patients with plague have an acute onset of fever, chills, and malaise. In the United States, approximately 80% have disease restricted to local lymph nodes. This bubonic form is characterized by exquisitely tender unilateral lymph node enlargement with overlying erythema and swelling. Fewer than 3% of such patients die. The septicemic form of disease is much more virulent, with high fever, pneumonia, and occasionally meningitis, and a fatality rate in excess of 70%. This is partly related to severe damage due to endotoxin release, and to the difficulty in making this diagnosis.[204]

Diagnosis

Plague should be suspected when the above clinical features occur in a patient with a history of residence in, or travel to, endemic regions during the warm months of the year. A history of flea bite, exposure to rodents, and the presence of lymphadenopathy, are important clues. The diagnosis is confirmed by culture (blood, lymph node aspirate, sputum), although 2–3 days or longer are often necessary to grow this organism, even in nutritious blood-containing media. Incubation at 28–30°C may favor growth. Serologic diagnosis is made by passive-hemagglutination or microscopic slide agglutination of appropriate antigens, but several weeks are required for antibody formation.

Treatment

Because of the fulminant nature of the septicemic form, treatment should be started with an aminoglycoside as soon as appropriate cultures have been obtained. These patients should also be isolated until pneumonia has been ruled out, since person-to-person spread by aerosol is a risk. Similarly, laboratory personnel should be warned about the possibility of this diagnosis, so that extra precautions can be taken.

Traditionally, streptomycin 20–30 mg/kg/day intramuscularly (divided twice daily) has been most effective. This treatment has usually been continued for approximately 5 days after defervescence. Other aminoglycosides are probably useful as well, although clinical experience with them is much more limited. Tetracycline and chloramphenicol are also effective, and chloramphenicol should be used in addition to aminoglycosides in patients who have associated plague meningitis. Incision and drainage of affected buboes and other abscesses are important. The response to therapy is not usually dramatic and an average of 5 days is often required before fever lysis.

Appropriate epidemiologic investigations should be carried out to identify the source of infection and to prevent spread. This is most essential when domestic rodent populations are involved, as epidemic spread can be rapid and virulent. Vaccine (Chapter 1) can be used to prevent disease in those whose occupations place them at high risk; however, current vaccine efficacy is far from complete and there is little reason to advocate widespread application to normal pediatric populations in the community.

Trichinosis

Epidemiology/Pathogenesis

Trichinosis is a systemic infection due to the parasite *Trichinella spiralis*. Although this condition has become infrequent in North America, outbreaks still occur and the infection remains of major importance in many areas of the world.[53] Approximately 150 cases/year are reported in the United States, with one or two deaths. The condition is acquired mainly through ingestion of raw or inadequately cooked (at less than 58°C) meat, especially pork. Strains resistant to freezing are found in bears and walruses in northern climates, making this an unreliable method for rendering food free from this parasite.[71]

After the larvae are consumed in meat, digestive enzymes in the gastrointestinal tract free the encysted parasite, which then develops into an adult worm. These worms produce many larvae within the patient's small intestine, which account for the nausea, vomiting, and diarrhea often noted. These larvae then enter the circulation (the migratory phase, lasting 1–7 days), encyst in striated muscles and may invade many other tissues.[228] It is this invasion that causes the serious manifestations, and even fatalities. Cell-mediated immunity is important in containment of these infections; as an immunocompromised patient with acute myelogenous leukemia exhibited intense invasion of the muscles.[144]

Clinical Manifestations

Approximately 2 weeks after ingestion of infected material (this can be as short as 3 days and as long as a month), the patient develops fever, nausea, vomiting, and diarrhea. It is not these signs, however, that suggest the diagnosis, but rather the severe periorbital and facial edema, myalgia, and eosinophilia that develop later. These patients may also have petechiae involving conjunctival, retinal, and subungual areas.[228]

If the migrating larvae invade the lungs, heart, or brain, life-threatening complications may ensue. These include consolidative pneumonia with hemoptysis, myocarditis with arrhythmias or infarction, and meningitis or encephalitis. Central nervous system involvement can also present as a brain abscess, which can be fatal.[94] The pathogenesis of these lesions is usually infarction and necrosis secondary to obstruction of small blood vessels, vasculitis, and toxic products of the larvae.

Diagnosis

The diagnosis of trichinosis is suggested most often by the constellation of periorbital edema, myalgia, and eosinophilia. When a compatible ingestion history is obtained (e.g., smoked sausage in southern Louisiana), the suspicion is heightened. Patients also manifest abnormal electromyograms, and elevations of the SGOT and creatine phosphokinase enzymes, indicative of muscle injury but not specifically diagnostic. The erythrocyte sedimentation rate, surprisingly, may be normal in some patients. The earliest method for the confirmation of this diagnosis is demonstration of the larvae in muscle biopsy material. After the second to third week of infection, serologic diagnosis becomes possible. The most frequently used serology is the bentonite flocculation test, which is positive in over 95% of cases. Counter-immunoelectrophoresis and ELISA methods are also useful.

Treatment

Muscular and subcutaneous tissue involvement is transient, and, although encysted organisms may produce inflammatory responses and remain viable for years, they are not capable of further invasion and multiplication, and the symptoms generally abide spontaneously. Hence, rest, analgesics, and antipyretics are sufficient in many cases. When the lungs, central nervous system, or heart are involved, however, considerable morbidity and even fatalities may occur. Hence, corticosteroid therapy should be administered to such patients in a dosage of approximately 1–2 mg/kg of prednisone/day. Concomitantly, thiabendazole 50 mg/kg/day, divided twice daily for a week, may also be effective against the parasite during the migratory stages (Chapter 2). Mebendazole is a useful alternative. Since this parasite is widespread in mammals, proper cooking and public health measures are most important in preventing this infection.

Malaria

Epidemiology

Malaria is one of the major infectious disease problems of the world. It is estimated that 300 million people are affected annually, of whom more than 1 million die each year in Africa alone.[349] The frequency of this disease is increasing, perhaps as a consequence of decreased effectiveness of methods for control of the mosquito vectors, travel, and the development of drug resistance by the malarial parasites. The Anopheles mosquito is the vector in the endemic areas as well as in the southern United States where sporadic cases, have been reported. However, of the Americans who are affected, the majority are travelers. Malaria can also be transmitted by blood transfusions,[255] by accidental intravenous inoculation of the parasite,[326] or through contaminated syringes used by drug addicts. Malaria in newborns also occurs secondary to intrauterine infection or as a result of transmission of infected red blood cells during delivery.

Because of their lack of immunity, travelers are at high risk, and should be advised to use mosquito netting and chemoprophylaxis, and to avoid heavily infected (predominantly rural) areas. The risk of acquisition of malaria varies with geography, altitude, and season, and may be related to genetic factors as well. Information about endemic areas and risks can be obtained from the Centers for Disease Control in the United States, state health departments, and World Health Organization offices. These sources can also provide information about chemoprophylaxis and the distribution of drug-resistant malarial parasites in various countries. Since malaria may be difficult to diagnose and can be fulminant, prevention is the best strategy.

Clinical Manifestations

Malaria has been called the "great imitator", because of the tremendous variation in clinical presentations observed.[161] The majority of affected individuals have a sudden onset of chills, fever, and profuse sweating. Myalgia, arthralgia, nausea, vomiting, diarrhea, and even unexplained coma may be present.[84] Fever lasts for a few days, followed by a variable symptom-free interval, which is generally about 24 h for *Plasmodium vivax, P. falciparum,* and *P. ovale,* and 48 h for *P. malariae.* These intervals should not be relied on as strict criteria to determine the species of the organism for purposes of treatment, however.

In addition to chills and fevers, splenomegaly and severe malaise commonly occur. Acute complications include anemia, hemolysis, and uncommon, but grave, developments such as cerebral, renal, and hematologic complications. Included in the latter are severe coagulation disturbances and acute renal failure due to massive hemolysis. Patients with cerebral malaria may present with extreme lethargy, seizures, or coma.

Malaria that occurs during pregnancy is particularly problematic because of the complexity of treatment with teratogenic and toxic drugs, and because of the effects of this infection on the newborn. Spontaneous abortion, low birth weight, and transmission of infection to the infant are possible sequelae. The onset of congenital malaria is usually manifest by fever and typically occurs at 3–8 weeks of age, although it may be delayed as long as 15 months.[267] These patients are often diagnosed as having "suspected sepsis" because of the nonspecific nature of the signs, including irritability, lethargy, anorexia, jaundice, and hepatosplenomegaly. Seizures, hemolytic anemia, thrombocytopenia, and hyperbilirubinemia are also frequently documented. The prolonged incubation period of congenital malaria is probably referable to passively acquired IgG antibody from infected mothers.

The differential diagnosis should include babesiosis, a rare intraerythrocytic protozoan infection[312] seen in New York, Massachusetts and elsewhere.[158] This condition can be transmitted by tick-bite as well as blood transfusion and is treated with a combination of clindamycin and quinine.[55]

Diagnosis

History of travel, blood transfusions, intravenous use of illicit drugs, or residence in an endemic area are important for suspicion of this diagnosis. Malaria should be considered in all patients with fever of obscure cause. The definitive diagnosis rests on demonstration of malarial parasites in thick and thin blood smears. These are usually obtained by finger prick and spread on carefully cleaned slides. Wright stain is adequate for screening these smears, although Giemsa stain is more useful for the determination of species which is important for treatment. Although serology can be used to detect past infection and asymptomatic infected blood donors, it is rarely useful in the diagnosis of acute infection.[149]

Treatment

The specifics of antimicrobial therapy for malaria are provided in Chapter 2. Generally, infection due to *Plasmodium vivax*, and *P. ovale* are treated with chloroquine for 2 days, followed by primaquine for 2 weeks.[159] Chloroquine is directed against the erythrocytic and primaquine against the exoerythrocytic parasites. Hence, primaquine is not necessary for *P. malariae*, for congenital infection and in infection acquired after transfusion or accidental inoculation.[37] Primaquine is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because of the risk of hemolysis.

Plasmodium falciparum is treated with chloroquine phosphate; however, chloroquine resistance is becoming a more frequent clinical problem.[290] Drug resistance to pyrimethamine/sulfadoxine has also developed in Thailand, South America, and Papua New Guinea.[73] In such cases, quinine can be used; however, recrudescence has been noted in as many as 25% of patients within 4 weeks of such treatment. These patients can be treated with quinine plus tetracycline or quinidine 30 mg/kg/day, divided q 8 h, for 7 days.[338] New drugs, such as mefloquine, which can be administered as a single 1 g oral dose, show much promise in drug-resistant cases.[148] This is an ever-changing story, however.[159]

Some of the complications of malaria require other therapeutic approaches. Hemolysis is often related to the percentage of parasitized red cells. When more than 10–20% of cells are infected, the risks of mortality are increased. Occasionally, exchange transfusion may be helpful in the treatment of such patients and in those with renal, cerebral, and coagulation complications.[176] Supportive care for renal failure, thrombocytopenia, electrolyte disturbances, and encephalopathy may also be required. A recent controlled study indicates that dexamethasone is not useful in the treatment of cerebral malaria.[331]

The treatment of congenital malaria is also complicated by the immaturity of the liver in these patients and the common coexistence of hyperbilirubinemia and other conditions. Moreover, there is a lack of experience with some of these drugs in newborns. Generally, chloroquine phosphate, 10 mg base/kg, is given orally, followed by 5 mg base/kg at 6, 24, and 48 h.[267] Patients with chloroquine-resistant strains may be treated with quinine 25 mg/kg/day, divided q 8 h, plus trimethoprim/sulfamethoxazole, 8 mg trimethoprim/40 mg sulfamethoxazole/kg/day, divided twice daily for 5 days. During pregnancy, pyrimethamine plus a sulfonamide may be safer for the fetus.[200]

In patients with malaria, blood smears should be repeated daily during treatment and for 48 h thereafter, to document eradication of the protozoa from the peripheral blood.

Prevention

The details of chemoprophylaxis are outlined in Chapter 2. Chloroquine phosphate is the standard prophylactic drug, but failures are seen, particularly with *P. falciparum*.[93] In areas where such strains are frequent, pyrimethamine plus sulfadoxine, or sulfone (dapsone), can be used.[46] Information about the endemicity of malaria and its drug-resistant forms is available from public health authorities and should be given high priority for travelers. There are no vaccines.[61] Currently prevention of malaria in nonendemic areas depends on public education and screening of blood donors, particularly to avoid donations from patients who have had malaria or recently lived or traveled in endemic areas.[149]

Trypanosomiasis

Epidemiology/Etiology

Trypanosomal infection in man can occur in two major forms. One, called African trypanosomiasis (African sleeping sickness), is caused by two subspecies of *Trypanosoma brucei*, namely *T.b. rhodesiense* or *T.b. gambiense*, depending on the geographic location.[222] The second form, American trypanosomiasis (Chagas disease), is endemic in Central and South America and is caused by *T.b. cruzi.*

The African trypanosoma are transmitted to man by insect vectors (the tsetse fly) from a wide variety of infected domestic and wild animals, but can also be transmitted by blood transfusion and transplacentally.[245] American trypanosomiasis is transmitted by the reduviid bugs. Infection during pregnancy may cause spontaneous abortion; however, congenital infection is uncommon.[21]

Clinical Manifestations

African trypanosomiasis most commonly presents with fever and with a raised, tender, erythematous nodule at the site of the insect bite. A morbilliform rash and lymphadenopathy may also be present, as may hematologic changes, including anemia, thrombocytopenia, and leukopenia. Meningoencephalitis is the most severe form of the disease, leading to the name "sleeping sickness," since patients most commonly manifest lethargy and encephalitic signs.

American trypanosomiasis can present as acute disease with much the same clinical manifestations mentioned above for the African variety.[245] Often, however, there is unilateral facial and palpebral edema and widespread lymphadenopathy in acute Chagas disease. Hepatosplenomegaly, gastrointestinal and central nervous system involvement may also be present. Chronic Chagas disease is potentially lethal because of invasion of the myocardium.[223]

Diagnosis

Epidemiologic history is useful in pointing to the possibility of this diagnosis, because the clinical signs are diverse and nonspecific. Trypanosomes can be demonstrated in smears of blood and cerebrospinal fluid in both types of trypanosomiasis.[129] Biphasic culture media may also be useful.[129] In addition, in African trypanosomiasis the cerebrospinal fluid (CSF) can have degenerated plasma cells (morula cells of Mott),[226] or an increase in IgM concentration.[106] Only mild degrees of CSF mononuclear pleocytosis are seen and the protein concentration can be either normal or elevated. Both diseases can also be diagnosed serologically by immunofluorescence or complement-fixation tests.[106]

Treatment

African trypanosomiasis is treated with suramin (Chapter 2). Melarsoprol is added when there is CNS involvement.[226] Since these drugs are fairly toxic, new investigational agents, such as α-difluoromethylornithine, may provide welcome additions to our therapeutic armamentarium.[9]

American trypanosomiasis is best treated using nitrofuran (Lampit^R) in a dose of 5–15 mg/kg daily for approximately 4 months.[199]

The mortality associated with the American form of trypanosomiasis is low, unless myocarditis is present. The African form is more severe, as the encephalitis can be fatal. These protozoa, much like those causing leishmaniasis and malaria, are widespread in endemic countries, and public health measures, including vector and reservoir controls, and early diagnosis and treatment have had little impact in curtailing infection.[222]

Opportunistic Infections

Etiology/Pathogenesis

Opportunistic infections can be defined as those caused by microorganisms that usually do not produce illness in normal hosts. Endogenous opportunists are often part of the normal flora, whereas exogenous ones are present in the animate and inanimate environment. Hence many of the bacteria that colonize our gastrointestinal tract, such as *Escherichia coli*, Pseudomonas,[140] and anaerobic streptococci, become opportunistic invaders when the host defense is decreased by surgery, trauma, or immunosuppression, or when these bacteria are introduced into a normally sterile site (e.g., peritoneum or bloodstream) (Table 12–12). Other organisms are acquired from the environment. Presumably, this is the source of atypical mycobacteriosis acquired by renal transplant recipients.[188] Patients who are hospitalized rapidly become colonized with *Candida albicans*,[205] which may then cause opportunistic infections.[135] Tri-

TABLE 12–12. Opportunistic Infections: Predisposing Factors

- Host abnormalities
  - Immune deficiency
  - Neutropenia
  - Surgery
  - Trauma
  - Burns
  - Eczema
  - Cancer/leukemia
  - Malnutrition
- Treatments
  - Immunosuppressive drugs
  - Antibiotics
  - Corticosteroids
  - Parenteral alimentation
  - Folic acid antagonists
- Environment
  - Hospital/nosocomial
  - Caretakers
  - Soil/dust
  - Laboratory
- Foreign bodies
  - Catheters
  - Ventilation tubes
  - Drainage tubes

chosporon,[115] and other fungi, and helminths such as Strongyloides,[138] may also become pathogenic in immunocompromised patients.

A myriad of common and unusual microorganisms of all classes have been described as opportunists. Some do not even have names, such as a gram-negative bacterium recently reported in a fatal case of septicemia in a patient with chronic granulomatous disease.[291] In other cases, common pathogens, such as respiratory viruses, Epstein-Barr virus, or Haemophilus, may cause uncharacteristic infections. Examples include Haemophilus septicemia in older patients[14] and prolonged parainfluenza virus pneumonia with extended periods of virus excretion. Polymicrobial infections and major coexisting infections are not uncommon in acquired immunodeficiency syndrome (AIDS) and in other immunosuppressed hosts.[335] Normal oral flora, such as *Capnocytophaga ochracea*, may also be involved.[98]

Cancer/Leukemia

Children with cancer present specific infectious problems. Fever in patients with acute lymphocytic leukemia is particularly worrisome because the infectious complications in these patients are frequent and severe.[256] Most of these infections are seen in children with neutrophil counts below 500/mm^3.[172] Infections during initial induction of remission are less frequently bacterial in origin than those seen during neutropenia.[246] *Pseudomonas aeruginosa* and *Staphylococcus aureus* are particularly prevalent in this population;[44] however, viral infections may be more frequent and prolonged in patients with acute lymphocytic leukemia as well.[50] Fatal mucormycosis has also been reported in teenagers with acute leukemia.[20]

In considering prevention of infection in children with leukemia several factors bear attention. Although infections are decreased by antimicrobial prophylaxis,[227] failures have been reported as a result of selection of resistant bacteria.[342] Another factor is the susceptibility of these patients to myelosuppression by trimethoprim and sulfonamides. Also important are compliance and patient tolerance when using oral antibiotic prophylactic programs and hospital isolation procedures. In fact, antimicrobial prophylaxis is most useful in granulocytopenic children with leukemia who are compliant with other aspects of their care.[260] Use of antimicrobials, immunizations, and isolation policies requires careful individualized strategies in children with cancer.[250]

Treatment of specific infections in these patients follows the same guidelines as that for other opportunistic infections. However, the neutropenic leukemic child with persistent fever might benefit from prolongation of initial antibiotic therapy and the addition of amphotericin B if the fever and neutropenia persist beyond 1 week, despite the fact that a bacterial or fungal pathogen has not been isolated.[257] Thus, children with cancer who have fever and neutropenia (fewer than 500 white blood cells/mm^3) require more antimicrobial therapy than we recommend for many other hosts. Careful hygiene, reasonable isolation procedures, surveillance cultures, and antimicrobial prophylaxis are important. Similarly, when such patients are seen out of hospital, careful attention to the etiology of each infectious episode should be given, before antibiotic therapy is begun. It is, therefore, justifiable to obtain cultures, and other laboratory studies more frequently in such patients, even with signs and symptoms that would suggest common self-limited infectious diseases in normal hosts.

One note of caution is warranted for these patients who develop pneumonia. Several antineoplastic drugs[15] and leukemia[162] may cause pneumonitis without associated infection.

Diagnosis

A high index of suspicion is critical to the diagnosis and management of opportunistic infection. The nature of the immune deficiency will often be a clue to the cause of infection. For example, fungal infections are common in patients with chronic granulomatous disease.[48] Infants and children with meningomyelocele, exstrophy of the bladder, burns, and eczema are at increased risk for opportunistic infection, as are hosts with conditions that interfere with clearance of bacteria, such as cystic fibrosis and hyposplenism. Conditions characterized by T-cell dysfunction make the host more susceptible to complicated infections due to viruses (particularly those in the herpes group), fungi (particularly Candida), protozoa (particularly *Pneumocystis carinii*), and facultative intracellular parasites (such as Mycobacteria, Listeria, Salmonella, and Nocardia). Opportunists are also seen in association with diseases that affect immune functions, such as diabetes mellitus, and with renal diseases, such as nephrotic syndrome.

Thus, a diversity of microorganisms may become opportunists in patients with immune and/or anatomic abnormalities (Table 12–13). Several other factors may compound the risks of opportunistic infection. These include surgery, foreign bodies (catheters, endotracheal tubes, etc.), antimicrobials, malnutrition, and parenteral alimentation.[17] Adrenal corticosteroids[340] and adrenocorticotropic hormone[42] (ACTH) may also lead to opportunistic infection with disastrous effects. The risk increases, with the degree of immunologic and anatomic impairment. One of the best examples of this is the patient after bone marrow transplantation who is often profoundly immunosuppressed and highly susceptible to opportunistic infection.[252] The same applies to renal[209] and liver transplant[289] recipients. Such patients, and those with leukemia, are often rendered neutropenic, which introduces yet another risk. When peripheral blood neutrophil concentrations are reduced below 500/mm^3, these

TABLE 12–13. Frequent Opportunistic Infections

Host Condition	*Infection*
Newborn	Cytomegalovirus, Staphylococcus, gram-negative enteric bacteria
Transplant recipient	Cytomegalovirus,[19] Staphylococcus, gram-negative enteric bacteria Candida Respiratory/enteroviruses *Pneumocystis carinii* Mycobacteria Coxsackieviruses[322]
Leukemia	Gram-negative enteric bacilli, esp. Pseudomonas *Pneumocystis carinii* Varicella
Hodgkin disease	Cryptococcus Herpes simplex
Cystic fibrosis	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Pseudomonas cepacia*
Nephrotic syndrome	*Streptococcus pneumoniae* *Haemophilus influenzae*
Congenital immunodeficiency	*Candida, Staphylococcus aureus*
IgA deficiency	*Giardia lamblia*
Hypocomplementemia	*Neisseria meningitidis*
Chronic granulomatous disease	Staphylococcus, Serratia Nocardia Aspergillus[45]
Burns	Staphylococcus Pseudomonas Fungi Herpes simplex, Varicella
Eczema	Herpes simplex, Varicella, *Staphylococcus*
Sickle-cell disease Splenectomy	*Streptococcus pneumoniae,* Salmonella
AIDS	*Pneumocystis carinii*[103] Herpes simplex,[298] Salmonella, cytomegalovirus
Agranulocytosis	Aspergillus, gram-negative bacteria
Malnutrition	Viral infections Parasitic infections (e.g., giardia, strongyloides)
Diabetes mellitus	Mucormycosis *M. tuberculosis*

patients have a much-increased propensity for gram-negative bacterial infection. To complicate matters even further, therapeutic agents and procedures may mimic pneumonitis and syndromes peculiar to transplant recipients, such as interstitial pneumonitis, remain largely unexplained.[24]

Shunt infections are discussed in Chapter 9 and infections in cystic fibrosis in Chapter 5.

Clinical Manifestations

The effects of opportunists range from acute life-threatening sepsis to persistent (but relatively benign) infection. Consequences of persistent viral infection may be grave, however. This is illustrated by the role of persistent viral gastroenteritis in the pathogenesis of enteric gram-negative bacillary sepsis in children with severe combined immunodeficiency.[147] A different consequence is the late development of malignancies in patients with persistent Epstein-Barr virus infections and underlying immunodeficiency diseases.[153]

Treatment/Prevention

Several approaches are used for the prevention and treatment of opportunistic infections.[258] For example, patients with severe neutropenia can be protected by protective isolation, which will reduce the frequency of infections in leukemic patients, although this has not been shown to prolong survival. Avoidance of granulocyte transfusions[122] and organ donations from infected individuals[336] may also decrease the risk of cytomegalovirus infection. In addition, prophylactic antibiotics can be given during the period of neutropenia,[160] and prophylactic oral acyclovir can prevent herpesvirus and cytomegalovirus infection in bone marrow transplant recipients.[99] Since antibiotics are among the predisposing factors for opportunistic infection, the risks and benefits of this approach must be balanced. Moreover, adverse effects, such as perception of bad taste, gastrointestinal upset, anorexia, and hematologic suppression (e.g., folic acid antagonism by trimethoprim/sulfamethoxazole must also be considered. A third approach is surveillance cultures to predict the etiology of opportunistic infections by advance characterization of the patient's respiratory, gastrointestinal, and cutaneous flora and their antibiotic susceptibilities, which allows a choice of the initial antibiotic regimens appropriate for acute septicemic episodes.[47] Active or passive immunization can also be used. Examples include varicella vaccination of children with leukemia and intravenous gammaglobulin to prevent cytomegalovirus infection.[265] Combinations of these strategies are most often employed in the management of patients at increased risk for opportunistic infections. Specific therapies are defined by the microbiologic cause and the immune defect.

Candidiasis

Epidemiology/Pathogenesis

Fungal infections in immunocompromised and normal patients are becoming more frequent as a consequence of an increase in complicated hospital-related procedures, host factors, and nosocomial infections. Among these, *Candida spp* are most prevalent. Multiple predisposing factors are important (Table 12–14), including antibiotics, intravenous alimentation, and immunosuppression.[214]

Intravenous alimentation is most risky when it is administered via a central venous catheter, but peripheral administration can also increase the risk for candidemia and focal infections. Fungus can grow in the parenteral alimentation fluid, at the point of insertion of the needle or catheter, and on the foreign body.[224] Venous catheters, even without parenteral alimentation, may be associated with candidemia, particularly if they are left in place for more than 3–4 days.[279] Other factors that have been implicated in the pathogenesis of candidiasis include tissue damage of any type, administration of adrenal corticosteroids, and cimetidine therapy.[323] The latter is thought to be related to decreased gastric acidity (acid is a host defense mechanism), enhancement of fungal growth, and the presence of gastrointestinal ulcers. In newborn infants maternal genitourinary candidiasis may be the source of infection.

Etiology

Candida albicans accounts for the majority of nosocomial mycotic infections in the perinatal period and in normal hosts with indwelling intravenous catheters. *Candida tropicalis* is particularly prevalent in patients with leukemia and in bone marrow transplantation recipients,[344] and *Candida parapsilosis* in patients receiving intravenous alimentation.[219] Other species of *Candida* (e.g. *C. krusei*) and other fungi are occasionally responsible as well.

TABLE 12–14. Factors Predisposing to Candidiasis

Antibiotics
T-cell immunosuppression
Surgery
Burns
Parenteral alimentation
Corticosteroids
Bowel perforation
Foreign body (catheters)

Clinical Manifestations

Focal Candida infections are relatively easy to recognize. Included among these are thrush, diaper and other types of dermatitis, and vaginitis. Most patients with systemic candidiasis, however, present only with fever and nonspecific signs, despite the fact that extensive lesions may be present in various organs (Fig. 12–5). These may include erythematous papular rashes and diffuse myalgia, a constellation that should suggest systemic candidiasis in patients at high risk.[142] More fulminant disease with disseminated intravascular coagulation may also occur in patients with *Candida albicans* septicemia.[254]

When the urinary tract is involved, all degrees of Candida infection may be seen, from focal infections of the meatus to invasive renal candidiasis with abscess formation. Fungus balls in the renal pelvis have also been reported.[163] Candiduria, without any proof of focal involvement, may also result from urinary excretion of Candida yeasts during candidemia. Patients with indwelling urinary catheters usually have transient candiduria associated with the catheter, although persistent cystitis may result as well. Other manifestations of candidiasis depend on the site of infection (Table 12–15).

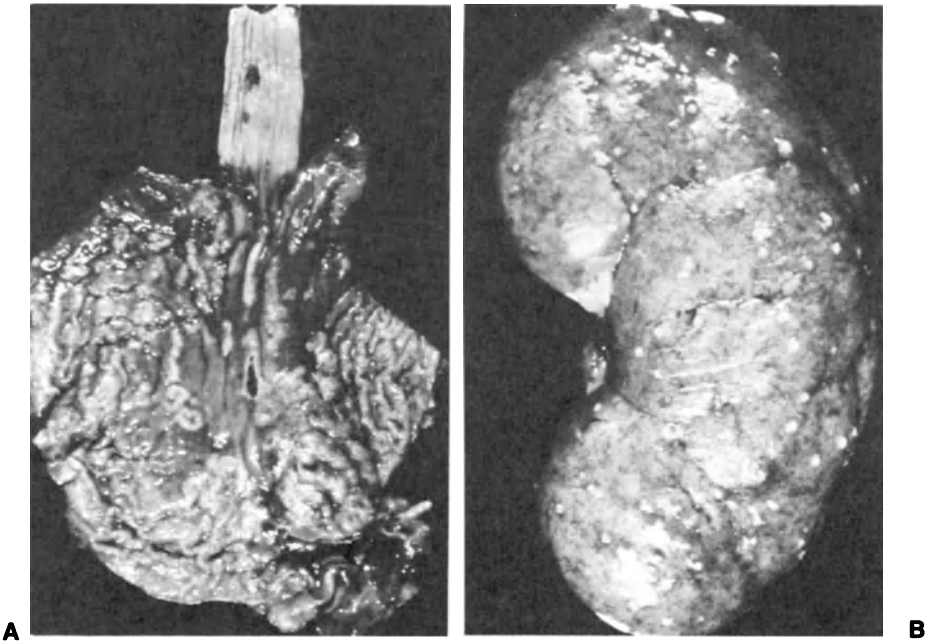

Figure 12–5. Widespread visceral involvement due to *Candida albicans* septicemia in an immunocompromised patient. **A**: Gastritis. **B**: Renal candidiasis.

TABLE 12-15. Manifestations of Candidiasis

- Thrush
- Diaper dermatitis
- Vaginitis
- Mucocutaneous (Chapter 7)
- Esophagitis
- Laryngitis[143]
- Candidemia
- Candiduria/renal candidiasis
- Endophthalmitis[119]
- Keratitis
- Endocarditis
- Thrombophlebitis[339]
- Meningitis
- Encephalitis[296]
- Arthritis
- Liver/spleen abscesses[329]
- Peritonitis
- Congenital candidiasis

Diagnosis

Candida spp are relatively large organisms, the yeast forms being approximately the size of red blood cells. Therefore, they are relatively easy to see in blood, urine, and focal lesions. Skin lesions should be examined by gram, potassium hydroxide, and/or Wright stains. This is particularly important in patients with pustular candidiasis of the skin, since clinical differentiation from bacterial and viral infections may not be easy. The Wright stain can also be used to examine smears of peripheral blood in high-risk patients with suspected fungemia.[300] Blood, urine, and appropriate cultures of focal lesions are also in order. Candida grows well at room temperature and at 37°C on nutritious media, including the usual laboratory blood agars. Selective media may be used to suppress normal skin or respiratory flora. Sabouraud's dextrose agar will support growth of these organisms, but as for other deep mycoses, more enriched media are desirable. Sabouraud's dextrose agar is most useful for culturing superficial dermatophytes.

How does one interpret candidemia, candiduria, or persistent fever without cultural evidence of Candida infection in high-risk hosts? This is an extremely difficult question that has plagued clinicians for years. It is not uncommon to find extensive visceral candidiasis at autopsy in a patient who had no clinical or microbiologic evidence of candidiasis during life. If, however, candidemia is detected, then serious systemic infection should be diagnosed, especially if the patient has Candida endophthalmitis,[224] or any other major focal manifestation of Candida infection. A possible exception to this conclusion is mucocutaneous lesions, which may be present in the absence of systemic yeast infection. Persistent candidemia without an indwelling vascular catheter, or persistent candiduria without a urinary catheter, should also be taken as evidence of systemic candidiasis.

Patients with candidiasis and malignancies, burns, and diffuse myalgia may have negative blood and urine cultures and minimal mucocutaneous involvement. Skin and/or muscle biopsy may be helpful to make the diagnosis in such patients.[178] Indirect and more experimental methods are being developed as well. These include passive hemagglutination[219] and ELISA[217] for the detection of circulating Candida antigens[136] or antibodies.[105,174]

Treatment

Correction of predisposing factors is one of the most important components of the treatment of Candida infections. Thus, removal of intravenous catheters, drainage of abscesses, discontinuation of antibiotics, and improved nutrition of the host are often effective. Antifungal therapy may be an essential adjunct in selected cases.

Topical therapy is indicated for patients with mucocutaneous candidiasis. When these patients also have candidemia or suspected systemic candidiasis, aggressive diagnosis and therapy are indicated, because the mortality risk can be extremely high. Amphotericin B is still the most active, although most toxic, agent available for the treatment of candidiasis. In many instances, it may be combined with 5-fluorocytosine,[43] which may permit a decreased dose (and, thereby, decrease toxicity) and increase the antifungal activity. This combination has been used effectively in newborns weighing as little as 800 g.[330] There is some risk, however, of suppression of the hematopoietic system when this combination is used, which is of particular concern in bone marrow transplant recipients and in patients with aplastic anemia or neutropenia.[62] Intravenous miconazole and oral ketoconazole should be considered in specific hosts after the acute episode of candidiasis is under control, and in those who cannot tolerate amphotericin B. Ketoconazole is particularly effective in mucocutaneous candidiasis, but can also be used for laryngitis, esophagitis and even osteomyelitis due to Candida.[63]

Prevention

Prevention is best accomplished by avoiding or improving underlying factors that predispose to candidiasis (Table 12–14). Other methods may also be used. This includes the oral administration of antifungal drugs for patients at high risk of Candida infection. Thus, leukemic patients receiving antibiotic therapy may be benefited by nystatin 400,000 units/day four times a day,[39] or amphotericin B, 50 mg orally four times a day.[79] Ketoconazole may also be effective for this purpose.[114] This approach should be taken in all high-risk patients receiving antibiotic therapy, corticosteroids, and, of course, in those with mucocutaneous candidiasis. Even when these preventive procedures are carried out, however, candidiasis remains one of the major opportunistic threats to immunocompromised patients.

Immune Deficiency

Etiology/Pathogenesis

The possibility of immune deficiency is often raised in patients with frequent or persistent infections (see Chapter 4). These deficiencies can be inherited, but may also be acquired because of congenital infections, such as cytomegalovirus,[108] or postnatally. Although the etiology in the latter group is unclear in many cases, the pathogenesis often includes a progressive loss of T-cells that are important in modulating other immune functions.[271] For example, this can be seen after Epstein-Barr virus infection.[113] Transient immune deficiencies are common during malnutrition, viral illness, and immunosuppressive chemotherapy, as well as after trauma and surgery.[179]

Clinical Manifestations

Identification of a patient with immune deficiency is not always easy. Recurrent infections are frequent in immunocompetent children in the first few years of life, particularly if there are school-age siblings in the home, or if crowding, day-care center environments, or other possibilities for exposure are frequent. Although minor abnormalities of immunity have been demonstrated in these children, it is unclear whether these are of primary importance.[16] It is estimated that six to eight respiratory infections per year are not uncommon under age 5, and five to six such infections commonly occur in young school-age children in temperate climate areas.[154] What are some of the clues then to the possibility of immune deficiency? These can be divided into historical (Table 12–16), clinical (Table 12–17), and microbiologic (Table 12–18) indicators.

If recurrent infections seem prolonged, atypical, or difficult to treat, and are associated with some of the clinical or microbiologic clues outlined in Tables 12–17 and 12–18, a more detailed history should be taken (Table 12–16). As new risk factors are being identified (e.g., the association of homosexuality with AIDS), more clues are added. Although the significance of severe infections and death in relatives in early life

TABLE 12–16. Immune Deficiency: Historical Clues

Family history of immune deficiency
Family history of unusual infections
Family history of collagen-vascular or allergic disease
Death of relatives in early childhood
Consanguinity of parents
Chronic candidiasis
AIDS or AIDS high-risk factors
Photosensitive rash
Rheumatoid arthritis
Recurrent/persistent infections (see Table 12–18)
Recurrent meningitis
Endocrinopathy
Splenectomy
Drug ingestion
Neonatal tetany/seizures
Child abuse[170]

seem obvious, the relevance of endocrinopathies, rashes, and arthritis may not be readily apparent. Thus, parents and physicians might not consider that isolated growth hormone deficiency might be related to a problem of recurrent infection. In fact, this has been described in association with X-linked hypogammaglobulinemia.[88] Other examples of endocrinopathies associated with immune deficiencies include chronic mucocutaneous candidiasis, and a recently described syndrome in males with diarrhea, diabetes mellitus, thyroiditis, and fatal infections.[264]

Conditions such as eczema are common in the general population, and, although associated with immune deficiency, they do not, by themselves, establish this diagnosis. In fact, most patients with eczema have normal neutrophil chemotaxis.[54] However, eczema is associated with recurrent infection and defective chemotaxis in a syndrome of hyperimmunoglobulinemia E and recurrent staphylococcal infection[124] and in the Wiskott-Aldrich syndrome. In the latter, thrombocytopenia, reduced serum concentrations of IgM, and eczema coexist. Other clinical clues to immune deficiency include gastrointestinal abnormalities, such as malabsorption, celiac disease, and recurrent diarrhea.[28] When these are associated with recurrent sinopulmonary infections, IgA deficiency should be suspected.[22]

Infections with specific pathogens, such as *Neisseria meningitidis*, suggest complement defects,[74] whereas infections with others, such as disseminated atypical mycobacteria, are linked with defective cell-mediated immunity[353] (Table 12–18). Sometimes profound abnormalities such as complement deficiency are associated with grave outcomes, as in patients with fulminant meningococcemia.[193]

TABLE 12–17. Immune Deficiency: Clinical and Laboratory Clues

Failure to thrive: decreased height and weight
Dwarfism[4]
Malabsorption

Onychomycosis
Thrush
Fine, sparse hair: Cartilage-hair syndrome
Alopecia[139]
Eczema
Oculocutaneous albinism/nystagmus: Chediak-Higashi syndrome[96]
Ataxia-telangiectasia[242]
Absent/sparse lymphoid tissue

Diffuse lymphadenopathy
Splenomegaly
Hepatomegaly
Absent thymus
Bony changes: osteochondropathy, cartilage-hair syndrome
Lipodystrophy

Lymphopenia
Thrombocytopenia
Anemia
Neutropenia
Hypouricemia: Purine nucleoside phosphorylase deficiency[308]
Hypocalcemia
} DiGeorge syndrome[49]
Cardiovascular defects
Repeated fractures: Osteogenesis imperfecta with hyper-IgE[30]
Down syndrome

Diagnosis

Diagnosis and characterization of immune deficiencies require extensive analysis of several components of the immune system (Table 12–19). This is important both for description of the susceptibilities and defects of the host, and for consideration of preventive and therapeutic strategies. Screening tests can be relatively simple, however. These should include the historical and clinical features mentioned above and some laboratory tests. Hence, the peripheral blood smear might reveal giant azurophilic granules in phagocytes, suggestive of Chediak-Higashi syndrome,[269] or blast cells, diagnostic of leukemia or lymphoma. Similarly, a routine hematologic assessment may reveal neutropenia, anemia, thrombocytopenia, or lymphopenia, all major clues to the presence of immune de-

TABLE 12–18. Immune Deficiency: Microbiologic Clues

Microbe	*Defect*	*Condition*
Staphylococcus aureus	Phagocyte	Job syndrome[67] Hyper-IgE syndrome
Neisseria meningitidis	Complement	
Streptococcus pneumoniae	Hyposplenism	Sickle-cell/other hemoglobinopathies
Streptococcus pneumoniae/ Haemophilus	Hypogammaglobulinemia	
Candida	T-cell	Combined immunodeficiency Chronic mucocutaneous candidiasis Nezelof syndrome
Herpes simplex Cytomegalovirus Salmonella	T-cell (helper)	AIDS
Epstein-Barr virus	B/T-cell	X-linked lymphoproliferative syndrome
Nocardia/Aspergillus Serratia *Chromobacterium violaceum*[196]	Phagocyte	Chronic granulomatous disease

ficiencies. Quantitative serum immunoglobulin and complement concentrations, and a test of phagocytic bactericidal activity, such as the nitroblue tetrazolium dye reduction test, can also be used to screen for immune deficiencies.

Microbiologic clues can also be very useful (Table 12–17). For example, recurrent staphylococcal infections suggest phagocytic, opsonic, or complement defects. Hence, an NBT test, chemiluminescence, serum immunoglobulin concentrations, and measurement of serum complement would be appropriate screening for such patients. Patients with recurrent meningitis, on the other hand, should have serum complement assayed, and patients with persistent Candida infections might have their T-cell numbers and functions assayed earlier. However, these clues are not specific and there is considerable overlap. For example, Haemophilus and pneumococcal infections are also associated with complement deficiencies, particular of the C2 component.[137] Complement also plays an important role in viral infections.[127] Patients with persistent Epstein-Barr virus infections should be evaluated for both T-cell immune defects and lymphomas.[113] Prolonged excretion of enteroviruses and persistent CNS enterovirus infection may also be features of agammaglobulinemia;[150] administration of specific high-titer antiserum may be useful in such cases.[334] Some of the components of the immune system and their dysfunctional expressions are presented in Table 12–19.

TABLE 12–19. Functional Classification of Immune Deficiencies

Immune Component	*Dysfunction*	*Test*	*Condition*
Phagocyte[221]	Decreased chemotaxis[91]	Boyden chamber	Hyper-IgE Chediak-Higashi syndrome Down syndrome Lactoferrin deficiency[27] X-linked deficiency[52]
	Decreased bacterial killing	Nitroblue tetrazolium dye reduction (NBT)	Chronic granulomatous disease Chediak-Higashi syndrome Glucose-6-phosphate dehydrogenase deficiency
	Decreased Candida killing	Leukocyte myeloperoxidase stain	Myeloperoxidase deficiency
	Recurrent fever, stomatitis, infections	Neutrophil quantitation	Cyclic neutropenia
T-cell	Recurrent/chronic infections	T-cell quantitation	DiGeorge syndrome
		T-cell function	Cartilage-hair syndrome Nezelof syndrome
B-cell	Recurrent infections	Immunoglobulin quantitation	
		B-cell quantitation	Hypogammaglobulinemia
		B-cell function	Dysgammaglobulinemia
		T helper cell quantitation	Transient hypogammaglobulinemia of infancy[299]
		IgE	Hyper-IgE syndrome

(*Continued*)

TABLE 12–19. Functional Classification of Immune Deficiencies (*Continued*)

Immune Component	*Dysfunction*	*Test*	*Condition*
Combined T- and B-cell	Recurrent/ chronic infection	As above	SCID syndrome Wiskott-Aldrich syndrome Ataxia-telangiectasia ADA deficiency
Complement	Recurrent infections	Serum complement assay	Hypocomplementemia[278]
IgA	Deficiency	Immunoglobulin quantitation Secretory IgA	Selective IgA deficiency[187]

Definition of a laboratory feature of immune deficiency should not be considered pathognomonic of a syndrome. For example, deficiencies in IgA and IgG may be transient in infancy and should not prompt aggressive therapy unless the patients are symptomatic.[22,317] Before embarking on immunologic therapy, consultation with clinical immunologists and complete characterization of the immune defects are important.

Down Syndrome

Patients with Down syndrome are prone to infection. Factors responsible include anatomic variation in structure of the upper respiratory tract, skull, and facial bones; pharyngoesophageal dysfunction; and poor personal hygiene. Moreover, institutionalized patients have more exposure to communicable infectious diseases and patients with heart defects, such as atrioventricular canal, may have right-to-left shunts with an increased risk of brain abscess. Other evidence points to genetically determined or acquired immunodeficiency. This evidence includes the predisposition of these patients to chronic hepatitis B antigenemia, an increased incidence of leukemia and other malignancies, and the frequent presence of autoantibodies in their sera.

Investigations of the immune status of Down syndrome patients show defects in the number and functions of both B- and T-lymphocytes[277] as well as dysfunction of the polymorphonuclear leukocytes.[156] The latter cells, as well as monocytes,[13] are often defective in chemotaxis, phagocytosis, and bactericidal activity. Many of these features, and an increase of chromosomal breaks in response to viral infections,[123] indicate an accelerated aging process. It has been postulated that Down syndrome patients are genetically predisposed to develop many of these immune abnormalities and that the basic mechanism is similar to that seen in aged individuals. The specific defects and genetic regulation of these immune functions have not been defined.

Treatment

Careful microbiologic assessment of each infection and febrile episode is a critical component of the effective diagnosis and management of many of the immune deficiency conditions. Relative states of immunologic immaturity, such as transient acquired immune deficiencies associated with corticosteroid therapy, rarely require specific immune therapies.[317] However, patients with these conditions should be protected from acute infections as much as is practical, should not receive live virus vaccines (for example, poliomyelitis may develop after oral polio vaccine),[284] and should be examined carefully and early in the course of suspected infectious diseases. Others with persistent defects such as agammaglobulinemia can be treated effectively with intramuscular or intravenous[345] immune serum globulin infusions.[307] Even this is not without risk, since rare complications of gammaglobulin therapy have been reported.[212] Children with chronic granulomatous disease, and some with neutropenia (e.g., leukemic patients receiving immunosuppressive drugs) may benefit from antimicrobial prophylaxis with trimethoprim/sulfamethoxazole.[333]

Although patients with severe immune deficiency can be protected from infection by strict protective isolation procedures,[341] this is not practical in most circumstances. A balance between the various needs of the patient and his family and the benefits of isolation is required. These considerations apply to treatments as well. Since many of these defects are variable in expression, physicians and parents should be wary of anecdotal reports of dramatic cures or paliations. For example, claims made for levamisole in the treatment of the hyper-IgE syndrome were disproved when subjected to placebo-controlled study.[66]

This description of immune deficiency is intended to be a preliminary guideline for the physician who encounters children with recurrent infections. When historical, clinical, or microbiologic features are suggestive, specific consultation is in order, since complete characterization of the defects and immunologic reconstitution (Table 12–20) require specialized knowledge and facilities. These treatments should not be undertaken lightly, since many are investigational and are potentially dangerous.[304] Nevertheless, successful immunologic reconstitution of a previously immune deficient child is one of the miracles of modern medicine.

TABLE 12–20. Therapy for Specific Immune Deficiency Syndromes

- Bone marrow transplantation
  - Severe combined immune deficiency
  - Wiskott-Aldrich syndrome
  - Cartilage-hair syndrome
  - Adenosine deaminase deficiency
  - Purine nucleoside phosphorylase deficiency
  - Selected phagocytic cell disorders[83]
- Thymus transplantation
- Immune globulin
  - Nezelof syndrome[297]
  - Congenital agammaglobulinemia
  - Acquired (e.g., Epstein-Barr virus) hypogammaglobulinemia
  - Prevention of CMV infection in patients with immune deficiency syndromes[345]
- Antifungal therapy
  - Chronic mucocutaneous candidiasis
- Leukocyte transfusion
  - Chronic granulomatous disease with severe acute infections resistant to other therapy[33]
  - Severe neutropenia with life-threatening progressive infection
- Plasma transfusions
  - IgA deficiency[187]
- Prophylactic antibiotics
  - Post splenectomy[194]
  - Chronic granulomatous disease[100]
  - Neutropenia

Acquired Immunodeficiency Syndrome (AIDS)

Epidemiology/Pathogenesis

Recognition of an acquired immunodeficiency syndrome in the pediatric population has followed on the heels of identification of this syndrome in adults.[145] The immune dysfunction involves both humoral and cell-mediated systems (Table 12–21), and the characteristics of the syndrome are extremely diverse.

Initially, this was thought to be a disturbance restricted to homosexual men, Haitians,[327] and intravenous drug abusers. However, the condition has also been described in male prisoners,[347] hemophiliacs[268], Dominicans, and infants. Affected newborns and infants have been small for gestational age, and born to Haitians,[152] promiscuous mothers, fathers with AIDS, or intravenous drug abusers.[282]

Exposure to blood products may also be important.[294] The blood may be derived from patients with the fully expressed syndrome,[5] or from donors with a milder form of the illness (e.g., manifest by fever, lymphadenopathy, and malaise). A considerable number of these patients have evidence of T-cell leukemia virus infection which may be the cause of AIDS.[92]

Clinical Manifestations

The clinical manifestations of pediatric AIDS include recurrent fever, lymphadenopathy,[97] hepatosplenomegaly, and failure to thrive.[240] Although these are nonspecific features, the prevalence of one or more opportunistic infections in these patients should suggest an immune deficiency (Table 12–21). Further questioning might reveal exposure to blood products or other high-risk contacts within the household. Persistent oral or mucosal candidiasis, persistent Epstein-Barr virus infection, disseminated mycobacterial infection, and *Pneumocystis carinii* are also clues to this condition. In adults, cytomegalovirus infection,[69] herpes simplex virus infections, cryptosporidial diarrhea, tuberculosis, toxoplasmosis, and Kaposi sarcoma are also noted.[347]

TABLE 12–21. Characteristics of Pediatric AIDS

- Immune dysfunctions
  - Anergy
  - Lymphopenia
  - Helper:suppressor T-cell ratio inversion
  - Hypergammaglobulinemia
  - Depressed cell-mediated immunity
- Infections
  - Candida
  - *Pneumocystis carinii*
  - Cytomegalovirus
  - Epstein-Barr virus
  - *Mycobacterium avium-intracellulare*
  - Salmonella
- Clinical features
  - Household contact with AIDS risk factors
  - Recurrent fever
  - Failure to thrive
  - Lymphadenopathy
  - Parotitis
  - Hepatosplenomegaly
  - Interstitial pneumonia
  - Small for gestational age

Treatment/Prognosis

The treatment and prognosis for this condition are difficult to discuss, in consideration of the broad nature of the immune deficits and the opportunistic infections described. The mortality rate among adults has ranged from 25 to 70% within a year of the clinical diagnosis. Thus far, similar mortality rates have been seen in affected infants. Early diagnosis and treatment may improve this prognosis. It is possible that immunologic reconstitution and early antimicrobial treatment may be useful. Definitive prevention and treatment rests on identification of the transmissible agent responsible for this syndrome which appears to be a human T-lymphotropic virus.[78,92a]

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13

Nosocomial Infections

Definition

Nosocomial infections are those patients acquire during hospitalization or in outpatient settings, such as during clinic visits.[15] Suppurative thrombophlebitis related to intravenous therapy is an obvious example.[22] These infections are a major problem. Approximately 5–6% of all patients acquire infectious diseases during hospitalization.[7] This figure may be as high as 25% in many neonatal intensive care units.[14] In one survey, acquisition of viral respiratory infections in infants and children prolonged hospitalization by an average of 9.3 days.[31] Mortality associated with nosocomial infections can be increased by as much as 14-fold, and costs by as much as 24%.[28] These statistics are of major importance to physicians, patients and their advocates, and hospital administrators. A variety of conventional opportunistic pathogens are lurking in the hospital environment, including newly evolved antibiotic-resistant (e.g., methicillin-resistant Staphylococcus[19]) or tolerant[21] forms. Such nosocomial infections may require special diagnostic and management strategies, such as vancomycin therapy for suspected or established staphylococcal infection.[27]

Surveillance/Epidemiology

Infection control epidemiology is a relatively new area of specialization[2] and many tools for the diagnosis and management of these complications are still in the testing stages.[32] In fact, some of the procedures formerly used to describe risks for nosocomial infection, and some control measures, have already been abandoned. These include the routine use of surface and air cultures as a surveillance method, and the use of fogging as a control method.[20]

The modern-day approach to nosocomial infections utilizes a multidisciplinary team, usually composed of an epidemiologist (this is often a specially trained nurse, physician, or technologist) working with several assistants in three major areas. These are (1) surveillance (description of the scope of the problem[s]), (2) control ("after the fact" measures in most cases), and (3) prevention. A multidisciplinary committee helps in the analysis of problems and implementation of control measures. There are ample fiscal and medical reasons to justify a high priority for these activities in any hospital. Infection control practitioners must be assigned adequate resources, power for implementation, mechanisms for education, and, in appropriate settings, recognition as an area of academic activity.

Effective surveillance for nosocomial infections involves daily rounds in patient areas, surveying the types and incidence of infectious diseases,[12] a review of positive microbiologic cultures (when practical, this should include viruses, chlamydiae, and mycoplasmae, as well as bacteria and fungi),[8] serologic tests (e.g., hepatitis, Epstein-Barr virus), and appropriate discussions with inpatient and outpatient unit directors. Antibiotic use and susceptibility testing are useful measures that may suggest means to control bacterial resistance in closed populations.[9] Monitoring of outpatient nosocomial infection rates is ideal but is often overlooked. Public health reporting and liaison are other important related surveillance activities. Environmental surveillance is usually indicated only in exceptional circumstances when a particular outbreak suggests a common source exposure, such as a recent series of Pseudomonas urinary tract infections traced to contaminated cystoscopy instruments.[30] Modern methods of strain identification can be used to characterize the epidemiology of nosocomial outbreaks and to suggest useful control and preventive remedies. This includes molecular definition of plasmid and microbial chromosomal DNA.[17]

When the results of surveillance are analyzed, it becomes quickly evident that nosocomial infections are frequent and continuing complications of medical care, and are increased in situations in which patient crowding, staff shortage, lack of handwashing facilities, and reduced awareness and motivation are prevalent. Other factors affecting the expression of nosocomial infectious diseases in infants and children include parenteral alimentation,[16] vascular[23] and urinary[10] catheters, neonatal intensive care, incontinence, the prevalence of common communicable diseases, and the season of the year (Table 13–1). For example, respiratory infections are particularly prevalent in the cold months,[25] whereas gastroenteritis is a year-round problem. Not surprisingly, community outbreaks of rotavirus and other enteric virus infections are reflected by an increase in nosocomial cases as well.[29] Nosocomial respi-

TABLE 13–1. Seasonal Variations in Nosocomial Infection

Season	*Predominant Cause of Nosocomial Infections*
Winter/spring	Respiratory syncytial virus Parainfluenza viruses Influenza viruses Rhinoviruses Adenoviruses Gastrointestinal pathogens
Fall/winter	Rotaviruses Respiratory pathogens
Spring/summer	Enteroviruses

ratory infections are probably the most frequent pediatric nosocomial problem in industrialized countries.[13] Observations of concurrent spread of multiple respiratory pathogens (e.g., rhinoviruses and respiratory syncytial viruses) are common.[33] In the summertime, enterovirus infections may present as nosocomial gastroenteritis, undefined fevers and rashes, or meningoencephalitis. These outbreaks have been particularly devastating in newborn units.

Most endemic nosocomial infections are acquired from flora present in the patient or in the hospital environment. Pathogens prevalent in the community reach hospitalized patients by two mechanisms. One is their carriage by newly admitted hospitalized patients. More significant is their introduction by visitors and caretakers who move among patients and between the community and the hospital. Occasionally, infections are transmitted between patients by inanimate objects, including instruments, medications, intravenous fluids,[16] and catheters. Nothing should be overlooked in analyzing the contribution of such vehicles and personnel in the transmission of nosocomial infections. Even antiseptic solutions may contain Pseudomonas,[26] and bandages have spread fungi.[6] Other conditions may mimic nosocomial infections. For example, contrast medium used for computerized tomography scanning has been found to be contaminated with endotoxin and has caused fever.[24]

Although the season of the year may determine the etiology of many of the minor but frequent nosocomial infectious problems, the host[3] may also be an important determinant of the type and severity of infection expressed (Table 13–2). Thus, patients with cancer, malnutrition, and other forms of immune deficiency are at high risk for acquisition of opportunistic pathogens, as well as the complications associated with these and common communicable infectious diseases. Patients with neutropenia are particularly at risk from Pseudomonas and other gram-negative pathogens, and their caretakers and visitors need to be aware

TABLE 13-2. Conditions that Place Hosts at Increased Risk of Nosocomial Infection

- Cancer
- Malnutrition
- Immune deficiency
- Chronic renal disease
- Hematologic disorders
  - Aplasia of bone marrow
  - Anemia
  - Neutropenia
  - Leukemia
- Splenectomy
- Nephrotic syndrome
- Congenital heart disease
- Tracheostomy
- Respiratory intubation/ventilation
- Catheters (vascular/urinary)

of this risk. These patients are particularly predisposed to infection with *Pneumocystis carinii, Legionella pneumophila,* cytomegalovirus, and multiply resistant bacteria. A major problem has also developed in many hospitals because of nosocomial infections with methicillin-resistant *Staphylococcus aureus.* Similarly, gram-negative bacteria such as amikacin-resistant Enterobacteriaceae can cause devastating nosocomial outbreaks.[5]

The location of the patient in the hospital may also play a role in determining the risk and type of nosocomial infection (Table 13-3). Hence, patients in oncology units may be exposed to Pneumocystis and cytomegalovirus infections more commonly than in other areas of the hospital. Respiratory pathogens are a particular risk in intensive care units where many patients are receiving ventilatory support and have tracheostomies or other ventilatory tube support systems. The patient who attends a hospital clinic may also be at increased risk of acquiring infection during the visit.[15] Examples include those exposed to a visitor or patient with varicella who inadvertently spends time in any clinic, or to an infant recently immunized with live polio vaccine, who accompanies and mingles with children in the immunodeficiency clinic. Life-threatening infections may result.

Control Measures

It is obvious that the most efficient way of preventing nosocomial infections is to avoid hospitalization. In fact, there is a trend away from hospitalization both for this reason, and because of costs and psychologic trauma. The longer a patient stays in hospital, the more likely he will

TABLE 13–3. Causes of Nosocomial Infections in Closed Populations

- Newborn nursery
  - Staphylococcus
  - Respiratory pathogens
  - Gastrointestinal pathogens
- Newborn intensive care
  - Enteric bacteria
  - Cytomegalovirus
  - Herpes simplex
  - *Staphylococcus aureus*
- Burn unit
  - Staphylococcus
  - Gram-negative bacteria including Pseudomonas
  - Fungi
  - Herpes simplex
- Intensive care
  - Respiratory pathogens/agents of tracheobronchitis
  - Catheter-related agents
- Transplant/oncology unit
  - Opportunists
- Hemodialysis unit
  - Hepatitis B
  - Cytomegalovirus
- Other "semiclosed" units e.g., clinic waiting rooms
  - Communicable diseases
  - Vaccine virus (e.g., poliovirus excretor)

acquire a nosocomial infection. Another determinant of the likelihood of infection is the communicability of the particular infectious disease. A partial list of some of the highly contagious infections of importance is included (Table 13–4).

Some of the general and specific control measures available for the prevention and control of nosocomial infections are listed in Table 13–

TABLE 13–4. Most Highly Communicable Infections

- Varicella zoster
- Pertussis
- Pneumonic plague
- Diphtheria
- Measles
- Influenza
- Meningococcal pneumonia
- Pulmonary tuberculosis with productive cough and positive acid-fast sputum smear

5. There are two stages to think about. One is the anticipation of spread of infection, which is the basis for prevention (i.e., isolation procedures, education, handwashing, etc). The second is the control of the infectious problem once it is detected. Although emphasis is needed for both strategies, a great deal of extra effort and motivation are required in the first instance. Although it is common sense to avoid exposing hospitalized patients to any infectious disease, visitors and caretakers often have respiratory and cutaneous infectious disease problems and are in close contact with patient populations. Similarly, breaks in handwashing technique and lack of sinks, soaps, and towels are major problems. In one survey, 21% of 541 nosocomial infections were due to bacteria found on hands of personnel.[18] Avoiding predisposing factors is extremely important in preventing infection. Use of scalp vein needles for peripheral alimentation[1] and strict guidelines for the use of other catheters are two examples.[4]

Once an outbreak is identified in a closed unit, a cohorting approach is often useful in preventing further spread. Ideal cohort procedures include separation of patients and personnel into at least three categories. These are (1) infected patients and their caretakers; (2) uninfected patients present in the unit at the time of identification of the infected patients, and their caretakers; and (3) newly admitted patients and their

TABLE 13-5. Nosocomial Infections: Control Measures

- General
  - Education
  - Decrease hospitalization
  - WASH HANDS
  - No visitors/caretakers with communicable diseases
  - Cohorting
  - Antibiotic use surveillance/control
- Screening patients and staff for:
  - Tuberculosis
  - Rubella
  - CMV
  - Varicella
- Immunization
  - VZIG: after varicella exposure
  - Hepatitis B vaccine: before exposure
  - Hepatitis B globulin: after exposure
  - Immune serum globulin: after exposure to measles, hepatitis A
  - Update immunizations
- Chemoprophylaxis
  - Acyclovir: to prevent herpes infections in transplant recipients
  - Rifampin: to prevent meningococcal and *Haemophilus* spread
  - TMP/SMZ: to prevent *Pneumocystic carinii* and other infections in neutropenic patients
  - Erythromycin: to prevent pertussis

caretakers. Division of the unit into three physical areas, three separate staffs, and three separate patient populations will interrupt the transmission of most nosocomial infections, unless communicating ventilation or shared equipment is contributory. Although this is ideal, it is often impractical. Compromises may, therefore, include combining personnel for the infected and uninfected patients in separate physical areas with careful handwashing and gowning technique between patient contacts. Other compromise approaches are also useful if careful attention to the details of cohorting are carried out.

Several control procedures are still investigational. This includes varicella vaccination of susceptible adult caretakers, which may prove to be a most useful approach to prevent both the disease and its spread. Similarly, experience with the use of acyclovir to prevent herpes infections in transplant patients may be applicable to other patients at high risk for acquisition of herpes group infections. Methods to suppress intestinal flora in children with leukemia undergoing induction chemotherapy are often associated with gastrointestinal upset, anorexia, and, occasionally, dangerous superinfections. Anorexia and weight loss with resultant malnutrition, and its immunosuppressive effects, are undesirable in an already immunocompromised oncology patient.

Specific isolation procedures can be defined for many pediatric infectious diseases. Guidelines are outlined in Tables 13-6 and 13-7. Others are available in the literature.[11] It is impossible to create rigid rules that would apply to all patients in all situations. Education about the mechanisms of spread of infectious diseases is as important as use of such reference lists. The definition of risk is often a difficult one, but is, in the final analysis, the rationale on which isolation procedures are based. Since the number of single rooms with separate isolation facilities and separate caretakers available in any hospital is limited, priorities for isolation should be established in relation to available resources and facilities. Two equations are useful in decision-making about specific isolation procedures. These are:

$$\text{Isolation benefit} = \frac{\text{communicability} + \text{severity} + \text{cost of nosocomial infection}}{\text{isolation risk}}$$

$$\text{Isolation risk} = \frac{\text{psychologic effects} + \text{nursing needs} + \text{emotional needs} + \text{cost}}{\text{efficacy of isolation procedure}}$$

Thus, it is obvious that one cannot consider any one factor alone in deciding on isolation techniques for a particular patient. For example, the use of a life island is an effective means of reduction of nosocomial colonization and infection in high-risk patients. This method, however, creates tremendous psychologic trauma and interferes with nursing and medical care in most situations. Although rates of infection are often reduced, other complications and the total effects on the duration of survival of such patients do not show a dramatic advantage of this system. Finally, education and awareness programs sound logical, and yet are often overlooked. The frustration of hospital epidemiologists in achieving these objectives is great. Yet an effective education awareness program in the area of nosocomial infection has reduced infection rates and nosocomial infection-associated mortality by approximately 50%.[3] Need I say more!

In addition to the aforementioned, employee health guidelines[34] should be implemented and enforced, and the following emphasized.

Special Units

Isolation procedures require particular attention and modification for certain closed populations, such as newborn nurseries, intensive care and burn units, oncology wards, and transplantation or neurosurgical areas. Of particular importance are:

1. Maintenance of optimal personnel-to-patient ratio.
2. Maintenance of adequate physical area around each patient.
3. Adequate handwashing facilities. It is recommended there be a foot-operated sink between each pair of beds.

Handwashing facilities

In all units should include sinks that are foot-operated, and supplied and maintained with foot-operated soap dispensers and with disposable towels.

Visiting Policies

Liberal and open visitation policies should be permitted throughout the hospital for pediatric patients, including those in isolation units. Education of visitors and individualization of policies can be effectively carried out to the psychologic benefit of the patients and their families.

Specific Recommendations

A system for isolation is recommended wherein the type of room and ventilation must be specified. This is done by reference to Tables 13–6 and 13–7 and by consultation for specific problems. It is then the responsibility of the attending physician or his/her delegate to order and adjust appropriate isolation procedures for each patient throughout the patient's hospitalization.

TABLE 13–6. Specific Isolation Guidelines

PRIORITIES CODE:

Single occupancy room:
1 = Highest priority for single room.
2 = Intermediate priority for single room.
3 = Lowest priority for single room.
0 = No single room requirement.

Air Pressure:
A = Highest priority for negative pressure room.
B = Intermediate priority for negative pressure room.
C = Low priority for negative pressure room.
P = Positive pressure required.
O = No special air pressure requirements.

					Priorities		
Condition	*Method of Spread*	*Incubation Period*	*Communicable Period*	*Type of Isolation*	*Single Room*	*Air Pressure*	*Comments*
AIDS	Blood/secretions?	?	?	Strict	1	O	Isolation varies with infection
Infection with antibiotic-resistant bacteria	Variable			Determined by site of infection	1	A	Negative pressure only necessary for respiratory colonization
Bronchiolitis	(See Respiratory syncytial virus)						
Burns	Direct, if infected			*Major burns*: Noninfected: Protective	1	P	
				Infected: Wound and skin	1	O	
				Minor burn: Wound and skin	0	O	

Campylobacter infection	(See Acute diarrhea)						
Candidiasis	Direct	Unknown	Duration of lesions	None	0	O	Meticulous hand washing
Chickenpox	(See Varicella)						
Conjunctivitis, nongonococcal	Direct	24–72 h	During active infection (until discharge ceases)	Secretion precautions	0	O	If nosocomial spread occurs, a single room with wound and skin precautions will be needed
Conjunctivitis, gonococcal	Direct		Until 24 h of appropriate antibiotic treatment	Wound and skin	3	O	Meticulous handwashing
Croup	Respiratory secretions, aerosol	Few days to 1 week	Duration of active disease	Respiratory	1	A	May combine patients with croup in the same room
Cytomegalovirus infection	Direct (urine, saliva, breast milk)	Unknown	Virus shed in urine and saliva months to years	Wound and skin, and oral secretions	2	O	Danger to pregnant women and some immunocompromised patients
Diarrhea, acute	Fecal-oral contact	Depends on cause	Until the specific pathogen is eliminated	Enteric	1	O	May combine patients with diarrhea due to the same cause

(*Continued*)

TABLE 13–6. Specific Isolation Guidelines (*continued*)

Condition	*Method of Spread*	*Incubation Period*	*Communicable Period*	*Type of Isolation*	*Priorities*		*Comments*
					Single Room	*Air Pressure*	
Diphtheria	Pharyngeal secretions	2–6 days	Until two negative throat cultures are obtained	Strict	1	A	
Ebola virus infection	(See Exotic infections)						
Encephalitis	Variable	Variable	See specific etiology	Secretion precautions until etiology clarified	0	O	See specific etiology
Epiglottitis	Pharyngeal secretions		Until 24 h of appropriate antibiotic treatment	Secretion precautions	1	C	
Exotic infections	Variable	Variable	Strict		1	A	
Giardiasis	Water, food, direct contact	Variable	Entire period	Excretion precautions	2	O	Emphasis on personal cleanliness and sanitary disposal of feces
Symptomatic incontinent							
Symptomatic continent Asymptomatic					0	O	
Hepatitis A or type unknown	Fecal-oral (urine, saliva, stool, blood)	2–7 weeks	2–3 weeks before jaundice, to 10 days after jaundice	Enteric and blood precautions	0	O	

Hepatitis B	Blood, blood products	6 weeks to 6 months	Blood infected from 6 weeks before onset, and can remain so for years in carrier	Blood precautions	0	O	Private room not required after diagnosis is confirmed, unless patient has bleeding complications
Hepatitis non-A, non-B							
Hepatitis B, carrier							
Herpes simplex (mucocutaneous) infection	Direct contact, and oral secretions	2–14 days	Until lesions are dry	Wound and skin, and secretion precautions	1	O	
Herpes zoster Localized	Direct contact	10–21 days	At least 5–7 days	Wound and skin	1	O	May mix with immunocompetent patients who have positive history or seroimmunity to chickenpox
Herpes zoster Disseminated	Direct, respiratory secretions	10–21 days	Duration of illness	Strict	1	A	
Immunocompromised patients	(See Neutropenia)						
Impetigo	(See Wound and skin infection)						
Infectious Mononucleosis	Respiratory secretions			Handwashing	0	O	Prolonged contact required for spread

(*Continued*)

TABLE 13–6. Specific Isolation Guidelines (*continued*)

Condition	*Method of Spread*	*Incubation Period*	*Communicable Period*	*Type of Isolation*	*Priorities* *Single Room*	*Priorities* *Air Pressure*	*Comments*
Influenza	Direct, respiratory secretions, aerosols	24–72 h	Variable 7–21 days	Respiratory	1	A	
Junin virus infection	(See Exotic infections)						
Leukemia	(see Neutropenia)						
Lassa fever	(See Exotic infections)						
Malaria	Insect vector and blood		Duration of illness	Blood precautions	0	O	
Marburg virus infection	(See Exotic infections)						
Measles (Rubeola)	Respiratory secretions, airborne, direct	10–14 days	Onset of catarrhal stage until 7 days after onset of rash	Respiratory	1	A	Isolation of contacts from 5th day to 14th day
Meningitis Meningococcal and meningococcemia, or of unknown etiology	Respiratory secretions	Usually 1–7 days	Until 24 h after appropriate antibiotic therapy	Respiratory	1	C	

Meningitis *H. influenzae*	Respiratory secretions	1–7 days	Until 24 h after appropriate antibiotic therapy	Respiratory	1	O	
Meningitis Other bacteria				Handwashing precautions	0	O	For group B *Streptococcus* refer to Table 13–7
Meningitis Viral (aseptic)		Variable	Duration of hospitalization	Excretion and secretion precautions	3	O	Risk of spread higher in newborns and infants
Mumps	Respiratory secretions, direct contact (saliva and urine)	14–21 days	7 days before illness until 9 days after onset	Respiratory	1	B	Isolate exposed patients from 7 days after contact until 21 days
Neutropenia (less than 500 neutrophils/mm^3)				Protective	1	P	Also recommended for other seriously immunocompromised patients
Parasitic infections	Variable	Variable	Entire period of infection	Variable excretion precautions	0	O	Emphasis on personal cleanliness and sanitary disposal of feces. (See Giardiasis)

(Continued)

TABLE 13–6. Specific Isolation Guidelines (*continued*)

					Priorities		
Condition	*Method of Spread*	*Incubation Period*	*Communicable Period*	*Type of Isolation*	*Single Room*	*Air Pressure*	*Comments*
Pediculosis	Contact			Handwashing precautions	0	O	Avoid contact with affected area and sharing of brushes, combs, etc.
Pertussis (whooping cough)	Respiratory secretions, airborne	5–21 days	Early catarrhal stage until 3 weeks after onset of paroxysms; *or* 7 days after starting erythromycin, or until culture negative (whichever is longer)	Respiratory	1	A	*CONTACTS*: Isolate 5 days after exposure until 21st day
Pneumonia Bacterial	Respiratory secretions	Variable		Respiratory	1	B	Until bacteria eliminated from infected site
Pneumonia Other	Respiratory secretions	Variable	Duration of illness	Respiratory	1	B	(Also see Influenza)
Poliomyelitis	Fecal, pharyngeal secretions	7–12 days	Duration of illness	Enteric	1	O	Virus may be excreted in feces 4–6 weeks

Rabies	Direct contact	2–6 weeks	Duration of illness	Strict	1	A	
Respiratory Syncytial Virus infection	Respiratory secretions, direct contact	Few days to week	Duration of active disease (average 6–7 days) virus can be recovered from immediate environment and fomites for 30 min to 7 h	Secretion precautions with gown	2	C	For similar disease (e.g., bronchiolitis) may cohort more than one child in appropriate room. Use separate gown for each patient
Rubella	Respiratory secretions, throat, CSF, urine in congenital infection		Extremely variable, up to 18 months	Respiratory	1	B	Danger to pregnant susceptible women. Can room with normal rubella immune patients
Rubeola	(See Measles)						
Salmonella infection	(See Diarrhea)						
Shigella infection	(See Diarrhea)						
Smallpox	(See Exotic infections)						
Staphylococcal scalded skin syndrome (extensive)				Wound and skin	2	O	

(*Continued*)

TABLE 13–6. Specific Isolation Guidelines (*continued*)

					Priorities		
Condition	*Method of Spread*	*Incubation Period*	*Communicable Period*	*Type of Isolation*	*Single Room*	*Air Pressure*	*Comments*
Streptococcal infection	Respiratory secretions, droplet	2–5 days	Until 24 h after therapy	Secretion precautions (oral)	2	O	
Syphilis, mucocutaneous, congenital, secondary	Contact with mucocutaneous lesions	10–90 days after infection	Until 24 h after treatment	Secretion precautions	3	O	
Tuberculosis, pulmonary (sputum positive *or* suspect)	Airborne, respiratory secretions	2–10 weeks	As long as infectious tubercle bacilli discharged (for approx. 3 weeks after initiation of therapy)	Respiratory	1	A	
Tuberculosis, sputum negative for AFB, extrapulmonary (with drainage)	Contact with drainage			Secretion precautions until drainage stops	3	O	Urine may be infective in renal tuberculosis
Tularemia, draining lesion	Rare spread from man to man	1–10 days	As long as lesion is actively draining	Secretion precautions	3	O	See Pneumonia, bacterial

Typhoid fever	Fecal-oral	1–3 weeks	For duration of excretion	Enteric	1	O	
Upper Respiratory infection (URI, common cold)	Respiratory secretions, contact	1–5 days	Duration of active disease (average 6–7 days)	Secretion precautions (oral)	2	C	Protect patients at high risk
Varicella	Direct, respiratory secretions, and airborne	10–21 day	From 4 days before rash and until all lesions are dry and crusted (approx. 7 days)	Strict	1	A	*Chickenpox contacts*: respiratory precautions 9th–21st day after initial contact
Wound and skin infections (*S. aureus*, St Strep. group A and others)	Direct	1–3 days	Until bacteriologically sterile	*Staph. aureus* and *Strep. group A*:			MAJOR: When infected area is not covered or dressings do not limit the purulent drainage LIMITED: Dressings cover and limit all purulent drainage
				Major: strict	1	A	
				Limited: wound and skin	2	O	

The system is summarized as follows and can be effectively listed on cards (to be posted on the door of a single room or on the patient's bed or isolette) in abbreviated form.

Definitions

Negative pressure ventilation: Mixed air supply with 100% exhaust to the outside. Direction of flow is from the corridor into the room.
Positive pressure ventilation: 100% of the air supplied from outside the hospital. Direction of air flow is from the room into the corridor.
Ordinary hospital ventilation: Mixed air supply and mixed exhaust with approximately equal flow.

Major Isolation Categories

1. Infections most contagious by the respiratory route: negative pressure ventilation in a single room.
2. Infections most contagious by direct contact: ordinary hospital ventilation in a single room.
3. Infections with mild to moderate contagiousness by respiratory contact: negative pressure ventilation if possible.
4. Infections with mild to moderate contagiousness by direct contact: ordinary hospital ventilation; double occupancy if single room is not available.
5. Patients at significant risk of acquiring nosocomial infection: positive pressure ventilation; single room (incubator for young infants).

In cases of infections due to the same cause, patients may share the same room and facilities.

Isolation and Precaution Techniques

Respiratory Isolation

Respiratory isolation is for patients with infection most contagious by the respiratory route. Masks are required on entry to the room and are discarded after exit. Hands are washed before patient contact and before exit. The face of a patient (or of his contacts) is covered with a mask, with appropriate handwashing, whenever he is outside the room. The door of the room is kept closed and the ventilation is under negative pressure. The supply of air is mixed, but the exhaust needs to be to the outside. A gown is used only when there is direct contact with the patient or immediate bedside materials.

Strict Isolation

Strict isolation is limited to those patients whose infections may be spread by multiple contact routes, or by air, and to patients with highly virulent, albeit rare, contagious diseases (e.g., diphtheria, rabies, varicella, etc.). A single room with negative air pressure is necessary and the room door must be closed. Masks are required on entry and discarded after exit. Hands are washed on entering and leaving the room. Gowns and gloves are required for contact with the patient or his bedside materials. Articles must be either discarded or bagged and sent to a central area for decontamination. Linens and soiled wastes should be double-bagged and labeled at the room door before removal. The patient should not leave the room during the contagious stage of illness. When this is absolutely unavoidable, all individuals should be well informed of the risks before transporting this patient from the room. Full precautions must be maintained throughout the process by transporters and all individuals handling the patient in the receiving location. Protection is also mandatory for other patients, personnel, and the public by priority use of the elevators.

Protective Isolation

Protective isolation is recommended for those patients with severe neutropenia (500 neutrophils/mm^3 or less), combined immune deficiency or suppression, and major burns (noninfected). A single room with positive air pressure is necessary and its door should be kept closed. All articles should be reserved for the exclusive use of that patient, and everything that touches the patient must be sterile, disinfected, or cleaned. Hands must be washed on entering and leaving the room. A clean gown and mask are required for each direct contact with the patient. Gloves should be used during invasive procedures. Modified and reduced forms of protective isolation may be used depending on the nature of the infection, condition and behavior of the patient, nursing and patient care needs, and facilities available.

Enteric Isolation

Enteric isolation is indicated for those patients whose infection can be spread by direct contact through the fecal-oral route. Neither special ventilation nor use of masks is required. To prevent cross-contamination, a single room is necessary for children who are incontinent and for any child whose behavior cannot be controlled. Hands must be washed on entering and leaving and after contact with stool or urine. Gloves may be worn at any time but are required for individuals with open cuts or lesions in contact with the patient or stool. Gowns should be worn when there is direct contact with the patient or bedside materials. Articles contaminated with stool or urine must be disinfected or discarded. Linens and diapers should be double-bagged at the door before removal from the patient's room. Patients who are taken from their isolated area should be dressed in clean gowns and covered with clean sheets, and the transporter should wear a gown.

Wound and Skin Isolation

Wound and skin isolation is indicated for patients with infections that are most contagious by direct transmission from wounds, localized lesions, specific body sites, and heavily contaminated articles. Single rooms are recommended for patients with infected major burns, mucocutaneous herpes simplex, and localized herpes zoster, and are desirable for patients with extensive scalded skin syndrome, cytomegalovirus infection, and wound infections due to *Staphylococcus aureus* or Streptococcus group A. No special ventilation is required. Hands must be washed on entering and leaving the area and as otherwise indicated during patient care. A gown should be worn during direct contact with the patient or his materials. Double-bag technique should be used in handling linens and dressings to be removed from the area. Special "no touch" dressing technique should be used during dressing changes, i.e., wear gloves, place soiled dressing into a plastic bag as removed, and touch wound or dressings only with gloved hand or instrument. In certain fungal wound infections it is also necessary to wear a mask. All special instruments must be discarded after use, or bagged, and sent to a central area for decontamination, disinfection, or sterilization. Before a patient is transported, the infected wound should be adequately covered, and when possible, fresh dressings applied. Transporters should wear a gown.

Secretion Precautions (Lesions and Oral)

Patients in this category do not require a single room or special ventilation. The patient can be handled as a noninfected patient, except that precautions are needed to prevent spread of infection to other patients and personnel from wounds and secretion-contaminated articles or from direct contact with infected secretions.

Lesions. These precautions apply to lesions from which there is discharge, and include handwashing before and after handling dressings or drainage from lesions, use of sterile supplies and equipment when changing dressings, double-bagging the soiled dressings and equipment, and using the "no touch" technique to handle dressings or discharge from the lesions. These techniques should be continued for as long as the lesion is considered infective.

Oral. Precautions are needed to prevent spread to susceptible individuals by contact with oral secretions. Disposable tissues should be used and, if the patient has nasotracheal suction or a tracheostomy, the suction catheter and gloves should also be placed into a plastic bag and appropriately disposed.

Excretion Precautions

Excretion precautions are indicated to prevent acquisition of infection by personnel and patients through direct contact with feces. Use of a single room and air control are not necessary. The diseases in this category are usually less contagious than those requiring enteric isolation. They can, however, be spread to susceptible individuals through the oral route by contact with excreta containing the organism. Strict attention is given to careful handwashing following any patient contact and especially after contact with excreta. Patients also should be instructed to wash after defecating. Disposal of excreta through modern sewage systems is appropriate and separate toilet facilities are not necessary.

Blood Precautions

Blood precautions are used to prevent spread of infection to patients and personnel through contact with blood or blood-contaminated articles when the patient has malaria, AIDS, arthropod borne viral fevers, or hepatitis. These diseases are associated with probable circulation of the etiologic agent in blood and precautions should be observed for the duration of the clinical illness. Precautions are also indicated with anyone who is HBsAg-positive (carrier). A single room is necessary for all patients with hepatitis, type unknown, but is not required after type B is confirmed, unless the patient has bleeding complications. There are no special requirements for air control. Hands must be washed on entering or leaving the patient's unit. Gloves should be worn for direct contact with the patient's blood (i.e., obtaining specimens, starting infusions, or handling blood-contaminated linens and equipment). Gloves should be worn during all direct patient contact by any person who has cuts, scratches, or lesions on his hands. Gowns should be worn when carrying out any procedure in which blood spills or splatters may occur. Blood-soaked linens should be double-bagged and labeled prior to disposal. Special precautions are required for handling of needles, syringes, and blood specimens. All blood specimens should be prominently labeled with the patient's diagnosis. Disposable syringes and needles should be used, collected in puncture-resistant, labeled containers, and sent in labeled bags to a central area for decontamination before discard. Used needles should never be recapped, bent, or broken to avoid accidental puncture.

Reusable syringes must be rinsed in cold water by a gloved worker, double-bagged, labeled, and sent for decontamination prior to reprocessing.

Personnel Guidelines

Respiratory Infection

Personnel with respiratory signs and symptoms (coryza, cough, sore throat, etc.) should wear masks while in direct patient contact, and change masks when they become moist; strict handwashing is also necessary between each patient. Such personnel should seek medical evaluation and care, and be relieved of patient contact responsibilities, if symptoms are prolonged and/or severe.

Herpes Infection

Personnel with herpes simplex lesions should avoid direct patient contact with the following categories of patients:

1. Newborn infants
2. Patients with eczema
3. Immunosuppressed patients
4. Patients with burns

In addition, these personnel should wear masks if they have lesions on or about the mouth, nose, or face, until their lesions are no longer oozing and well into the drying phase. Strict handwashing procedures should be followed in all cases.

General Considerations for Newborns (Table 13–7)

Nosocomial epidemics are frequent in newborn units. A recent outbreak of polymicrobial bacteremia involved 20 newborns in an intensive care area, with two deaths.[16] Case-control studies revealed the most likely cause was a contaminated lipid emulsion. These units are continually high-risk areas for such outbreaks.

Table 13–7 is intended to provide guidelines for the isolation of newborns with communicable infections. Although private rooms are recommended, they may not always be available. In such circumstances, the patient should be placed in an incubator and moved to an area of the room with less traffic, with adequate handwashing facilities, and with as much space around the incubator as possible. In addition, the appropriate isolation card(s) should be affixed to the incubator and around the perimeter of the isolation area.

TABLE 13–7. Isolation Guidelines for Newborns

PRIORITIES
CODE:

Single occupancy:
1 = Highest priority for single room.
2 = Intermediate priority for single room.
3 = Low priority for single room.
0 = No single room requirement.

Air Pressure:
A = Highest priority for negative pressure room.
B = Intermediate priority for negative pressure room.
C = Low priority for negative pressure room.
P = Positive pressure required.
O = No special air pressure requirements.

					Priorities		
Condition	*Method of Spread*	*Incubation Period*	*Communicable Period*	*Type of Isolation*	*Single Room*	*Air Pressure*	*Comments*
Conjunctivitis gonococcal	direct		Until 24 h of appropriate antibiotic treatment	Wound and skin	3	O	Meticulous handwashing
Conjunctivitis nongonococcal	direct	24–72 h	Duration of active infection (until discharge ceases)	Secretion precautions: lesions	0	O	If nosocomial spread occurs, a single room with wound and skin precautions will be needed

(*Continued*)

TABLE 13-7. Isolation Guidelines for Newborns (*continued*)

Condition	*Method of Spread*	*Incubation Period*	*Communicable Period*	*Type of Isolation*	*Priorities*		*Comments*
					Single Room	*Air Pressure*	
Cytomegalovirus infection	Direct (urine, saliva, breast milk)	Unknown	Virus shed in urine and saliva months to years	Wound and skin and oral secretions	2	O	Danger to pregnant women and susceptible prematures
Diarrhea	Fecal-oral contact	Depends on etiologic cause of diarrhea	Until symptoms resolved and the specific pathogen eliminated	Enteric	1	O	If necessary, may cohort
Hepatitis A or type unknown	Fecal-oral (urine, saliva, stool, blood)	2–7 weeks	2–3 weeks before jaundice to 10 days after	Enteric and blood precautions	1	O	
Hepatitis B, Hepatitis non-A, non-B Hepatitis B, carrier	Blood, blood products	6 weeks - 6 months	Blood infective 6 weeks before onset and for years in carrier	Blood precautions	0	O	Private room not required after diagnosis is confirmed, unless patient has bleeding complications
Herpes simplex (mucocutaneous) infection	Direct	2–14 days	Until lesions are gone	Wound and skin	1	O	

Necrotizing enterocolitis	(See Diarrhea)						
Rotavirus infection	(See Diarrhea)						
Rubella (congenital)	Respiratory secretions, direct rect throat, CSF, urine		Extremely variable up to 18 months	Respiratory	1	B	Danger to susceptible pregnant women
Streptococcus, group B infection	Direct contact	1–5 days	Until 5 days after therapy	Wound and skin	2	O	
Syphilis, mucocutaneous, congenital	Direct contact	10–90 days after incubation	Until 24 h after treatment	Secretion-oral	3	O	Spread via open lesions and nasal secretions (congenital syphilis)
Toxoplasmosis	Contact with cats, ingestion of raw meat, intrauterine		Man-man spread not reported	None	0	O	Handwashing

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